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Clinical Aspects of Gastric Secretion

By Arthur L. Bloomfield, M.D., F.A.C.P.,
San Francisco, California

THE study of gastric secretion in man may be approached from either of two standpoints. First, there are the problems dealing with the mechanism of the formation of the various constituents of the gastric juice and with the variations of these constituents under "normal" or "average" conditions. Here we do not seek that utility which is implicit in clinical observations; we deal with a phase of animal (human) physiology. But there is another aspect which is of importance to the pathologist and to the physician, namely, the correlations which may exist between aberrations of secretion and disorders of structure or function of the stomach. This study is practical and empirical and it serves no purpose unless its results aid in diagnosis or lead to useful therapeutic action.

Ideas about the physiology of gastric secretion in man have been based largely on the results of animal studies. The pouch preparations of Pavlow and of Heidenhain modified by a host of pupils and followers still represent the usual method of study, and while occasional observations on men with gastric fistulas such as those of Beaumont and more recently of Carlson have been recorded, most of the human studies have been carried on by clinicians with a view to developing diagnostic methods in disease. Physiologists working in this domain, curiously enough, seem disinclined either to use the human subject or to accept as sound the results of human studies, and a scrutiny of the recent literature suggests that those dealing with men on the one hand, and with dogs on the other, seem destined, like the parallel lines of Euclid, never to meet on common ground. None the less, we believe that by proper methods accurate measurement of the gastric secretions of men can be made and it is the present purpose to summarize the results of such studies both in normal people and in disease.

Presented at the San Francisco Meeting of the American College of Physicians, April 4, 1932.

From the Department of Medicine, Stanford University Medical School.

Methods

Since the popularization of the stomach pump sixty years ago the gastric juices have been readily accessible for study, but bitter debates have been carried on as to what sort of stimulus is most appropriate for promoting a flow of juice. That it should be some sort of meal which the subject consumes seems to be agreed

upon by common consent despite the fact that such a procedure defeats its purpose at the start; pure secretions are then unobtainable and one recovers for study gastric juice mixed with a variable and uncertain quantity of foreign substance. Indeed the very essence of the procedure of the animal physiologist—the expedient of the isolated gastric pouch—was designed to evade this difficulty and to allow the collection of uncontaminated secretions. Within recent years pharmacodynamic substances, such as histamine, which powerfully stimulate gastric secretion and which can be administered parenterally have become available so that pure gastric juice can now be obtained from men under standard conditions. But in practice most clinical workers cling with almost sentimental tenacity to the idea that a meal of some sort must be eaten if the stomach is to reveal its true activities. The principal argument has been that histamine is unphysiological and that to test its function one must give the stomach normal work to do—namely, a meal. From the standpoint of the physiologist such a claim is, of course, absurd. One need only to recall that the standard stimulus used in animal physiology—the electric current—is one which the animal in nature does not encounter at all. Furthermore, who is to say what sort of a meal would constitute the normal for any particular person; certainly there is no reason to regard the usual doses of bread, gruel or meat as especially suitable. Rather it would seem important to abandon these anthropomorphic concepts of gastric activity and to invoke the basic principles which must be fulfilled with any adequate functional test. The matter has been discussed in detail elsewhere,[1] but briefly, it may be said that the stimulus must be a uniform one capable of repetition under approximately identical conditions, that it must impose stress on the function to be tested and that in practice it must yield useful information. The ordinary test meals clearly fail to meet these specifications; they impose no tax which will bring out the maximum secretory capabilities of the stomach, they approach a standard stimulus only very roughly and the variable mixtures of food and gastric juice which are obtained for analysis are unsuitable for quantitative studies. Histamine, on the other hand, has made possible accurate estimations of gastric secretion; it fulfills all the criteria which have been enumerated above. If the drug is given hypodermically, pure gastric juice may be withdrawn from the stomach just as from a Pavlow pouch. The actual technic of the procedure has been amply described[2] and need not be reiterated here. Suffice it to say that if the total gastric secretions are aspirated by continuous suction after a suitable injection of histamine a constant sequence of events takes place in normal people. For the first few minutes there is no evidence of increased secretion but during the second ten-minute period the volume of juice is definitely increased and during the third or fourth period a maximum flow is attained which then gradually subsides. Coincidently with increased rate of secretion the titratable acidity rises and reaches a peak, usually after 20 to 30 minutes. The maximum

amount of juice secreted during any one ten-minute period and the highest acidity attained after a standard dose of histamine are values which may be taken as substantial indices of the secretory capability of the stomach in question. If the technic of aspiration is carried out properly, beautiful smooth curves are obtained which reflect the accuracy of the procedure. A few sample curves are shown in figures 1 and 2.

Clinical Physiology

The first problem was to work out normal standards to be used as a basis for comparison with the results in disease. Details of such studies have been reported elsewhere.[3] Perhaps the most striking fact which emerged was the wide variation both of acidity and of volume of secretion which existed in a group of healthy people without demonstrable gastric disorder. To be sure, the majority of the values fell in a fairly narrow range but there were sufficient exceptions to make it clear that no rigid standards of normality can be laid down; indeed there are a considerable number of apparently normal individuals who secrete no juice at all but only a little mucus. All that one can do then is to plot distribution curves and to assume that the nearer the values in a test case lie to the mean the more likely they are

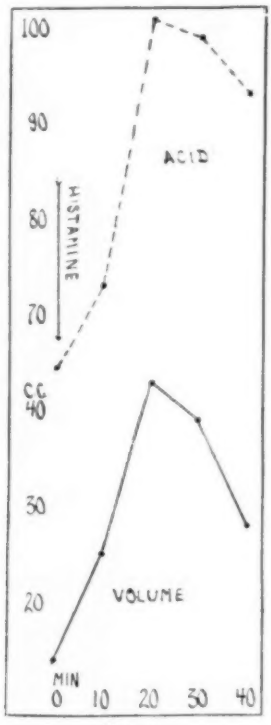

Fig. 1

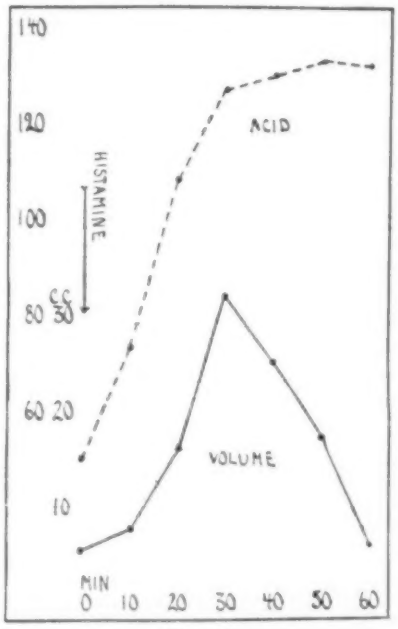

Fig. 2

Figs. 1 and 2. Curves showing volume of secretion and acidity at various intervals after histamine stimulation. (Bloomfield and Polland, Jr. Am. Med. Assoc., 1929, xcii, 1508.)

to be normal. Such distribution curves of acidity and of volume of secretion based on the findings in 100 normal people are shown in figures 3 and 4. It is seen that the largest amount of juice secreted in a ten-minute period fell within the limits of 21 to 35 c.c. in about one-half of the subjects, but values from 5 c.c. to 70 c.c. were encountered. So, too, with acid three-fourths of the values lie above 100 but some normals yield much lower figures. Other interesting facts are the steady decrease in average volume and acidity with advancing years, and the differences in the sexes which have been pointed out by Vanzant.[4]

These findings in normal people lead to certain reflections as to the physiological significance of gastric secretion; clearly the process is of much less importance to the organism than is, for example, the secretion of urine or the regulation of the acid-base balance. Indeed, one may reasonably take the view that gastric digestion in man is a matter of no great consequence and that gastric secretion has failed to develop as a highly standardized process; some mammalian species, such as the rat, even though omnivorous, possess no acid gastric secretion at all (Polland[5]), and certainly many people though devoid of gastric juice maintain perfect health and nutrition and suffer no digestive symptoms.[6] The breaking down of food is adequately accomplished by the intestinal juices and experimental proof of this mechanism has been obtained by Hines in this clinic. This concept is of prime importance to the clinician because, as we shall point out later, if the process of gastric secretion is normally somewhat variable it will clearly be difficult to interpret the findings in disease.

Basal Secretion

So far we have considered the response of the stomach to a purposeful stimulus. But the question of gastric secretion can be viewed from another angle, that of the fasting or basal se-

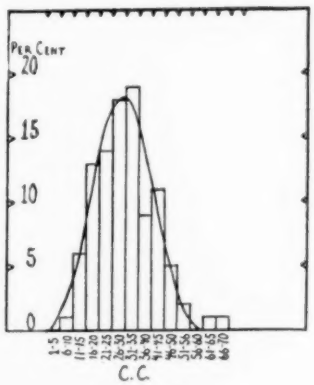

Fig. 3

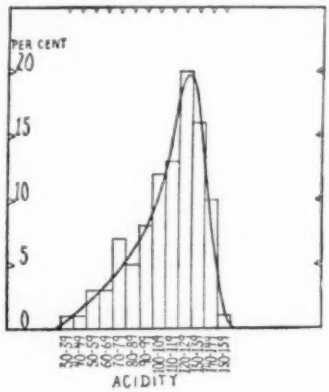

Fig. 4

Fig. 3. Distribution of highest ten-minute volumes of secretion from one hundred normal people (after histamine). (Polland and Bloomfield: Jr. Clin. Invest., 1931, ix, 651.)

Fig. 4. Distribution of highest acidity reached after histamine stimulation by one hundred normal people. (Polland and Bloomfield: Jr. Clin. Invest., 1931, ix, 651.)

cretion. Even with the subject at rest and without food one must suppose that the secretory mechanism is still under the influence of stimuli whether mediated through the autonomic nerves, or by hormonal or other influences. Such is actually the case, and there have recently been recorded systematic observations on the gastric juice produced by people brought as nearly as possible into the "basal" state and disturbed only by the passage of the aspirating tube.[7] Under these conditions it was found that most normal people secrete some gastric juice; it may vary in amount up to 20 or more c.c. per ten-minute period and the acidity frequently is over 100 (titratable, phenolphthalein). Furthermore, the type of juice obtained from any person is much the same on successive examinations; it is, perhaps, an expression of the activity of his autonomic nervous system. When the basal secretion is abundant and highly acid there is but little change after an additional stimulus, even such a potent one as histamine. It may turn out that the basal gastric secretion can be correlated not only with other physiological characteristics but with disease as well, but as far as we know adequate studies on this point have not yet been made.

Pepsin

Many attempts have been made to develop clinical methods for measuring pepsin but no very satisfactory procedure has been devised because of the inherent difficulties of ferment titrations. Polland and Bloomfield[8], using a more accurate modification of previous methods, measured the concentration of pepsin and the total output in normal people and in disease. Roughly there was a parallelism between the presence of pepsin and the normality of the juice in other respects; that is, whenever acid was abundant there was always an adequate amount of pepsin. In some patients with anacidity pepsin was still detectable but in insignificant quantities. In no case have we found an abundance of pepsin in the presence of a deficiency of acid or vice versa. Measurements of pepsin serve no purpose, therefore, in practical clinical work even though of interest from the standpoint of the physiologist and chemist.

Clinical Applications

We may now turn to the actual clinical uses of measurements of gastric secretion and again it must be emphasized that any conclusions which are reached are essentially empirical. It is with the fruits of practical experience and not with theoretical questions that we now have to deal, and it may be said in advance that regardless of method the sum total of information of help in dealing with patients is meager. The histamine test has the great advantage of at least yielding accurate data but the application of these data unfortunately is limited. Rearrange one hundred pennies as one will, no more than a dollar will emerge. It is essential that this be made clear because from time to time articles appear which becloud the real issue insofar as they defend, by special pleading, one or another procedure such as the Ewald or the fractional gruel meal and give an erron-

eous impression as to the value of the information to be obtained from any test of gastric secretion.

More in detail, the first question which presents itself is whether there is any correlation between the amount and acidity of the gastric juice and the patient's symptoms. This question must be answered in the negative. There is no feature of the patient's complaints which enables one to predict whether his secretion will be scanty or abundant, highly acid or poor in acid. It is true that the type of indigestion which is common in patients with peptic ulcer is often associated with the presence of large amounts of highly acid juice but so many people with identical symptoms have neither ulcer nor high acid that no valid correlation can be made. Furthermore, many individuals with no symptoms at all turn out to have an abundant highly acid secretion or perhaps no secretion at all. The syndrome of "hyperacidity" of the older writers had better, then, be altogether abandoned, especially as recent studies of the mechanism of indigestion show that the symptoms are brought about by motor and not by secretory difficulties.[9]

Turning next from digestive symptoms to anatomical lesions, is there any relation between disease and the type of gastric juice? Under three conditions only have we found a valid correlation. First, in true Addisonian (pernicious) anemia absence of gastric secretion, is, as everyone knows, an almost constant finding. Hence a normal stomach juice weighs heavily against this type of anemia although severe anemias of other varieties (hypochromic) frequently co-exist with gastric anacidity. Secondly, with peptic ulcer, especially duodenal ulcer, both acidity and volume of secretion are usually above the average, and while this is not invariably true it is so frequent that *in a doubtful case* scanty juice of low acidity or absence of acid point strongly away from ulcer as the correct diagnosis. High acid, on the other hand, while *compatible* with ulcer does not make the diagnosis since many normal people have just as high acid values as are found in ulcer cases. With cancer of the stomach one finds just the reverse; anacidity or low acid is present in such a preponderance of the cases that in a doubtful case—say an obstructive lesion of the pylorus—high acid would point away from cancer and towards a benign lesion. Aside from these three specific diseases—pernicious anemia, ulcer and cancer—it must be admitted that in practice studies of gastric secretion have little meaning and as time goes by we find ourselves passing the tube with less and less frequency. As with many other "special tests" in medicine examination of gastric secretion should be done not as a purposeless routine but to answer a definite question and a question which the test is capable of answering. Thousands of gastric analyses—most of them probably inaccurately executed—are done each year without the remotest possibility of serving any useful purpose; whether the acid is high or low or for that matter absent, nothing is usually brought out which either helps with diagnosis or leads to constructive action.

The reader is already thinking of

the many reports on all sorts of diseases—diabetes, hyperthyroidism, arthritis, acne, gall bladder disorders, etc. etc.,—in which it is claimed that some characteristic aberration of gastric secretion exists. These claims we have been unable to confirm if an adequate technic is followed and if proper controls with due consideration of the age of the patients and other factors are used as a basis for comparison. Distribution curves of acidity and volume of secretion from a large number of miscellaneous cases which demonstrate this fact will be published shortly (Polland).

Finally, a question of interest is whether disease of the stomach leads to alterations of the gastric secretions. Is, for example, a cancer, as it grows associated with progressive diminution in the flow of juice and in its acidity? Hurst[10] and Polland and Bloomfield[11] have presented evidence that such is not the case, nor is there any reason to believe that ulcer leads to increased secretion of acid. Rather is it true that ulcer tends to occur in people who to begin with secrete an abundant highly acid juice just as cancer usually occurs in those who already have a "gastritis" with deficient secretion.

Summary

Because of the wide variations in gastric secretion which are found in healthy people it is difficult to draw conclusions of diagnostic value in patients. This difficulty is enhanced by the crude test meal methods which are usually employed. In practice, measurement of gastric secretion is helpful in the diagnosis of pernicious anemia (and perhaps certain types of hypochromic anemia), of gastric and duodenal ulcer, and of cancer of the stomach. The "routine" employment of test-meals, even in the case of patients with indigestion, is useless, whereas an occasional well conducted measurement of gastric secretion performed to aid in solving a special diagnostic perplexity is sometimes of the greatest value.

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Standards of Normal in Gastric Secretion

By Walter C. Alvarez, M.D., F.A.C.P.,
Rochester, Minnesota

After approximately fifty years of stomach pumping and busy filling of archives with countless papers on gastric analysis, it would seem as if everything worth doing must have been done over and over again. Actually years of search through the enormous literature led me finally to the conclusion that most of the work on standards of normal which should have been done at the beginning has never been done, or at least, has never been done with enough material or with the technic that would satisfy a modern biometrician.

The value of one gastric analysis. For instance: What is the value of one gastric analysis? Through what limits is the acidity of the gastric contents of an individual likely to vary from day to day? Ordinarily when a physician gets a report back from the laboratory he is likely to assume that the figures, 40 free and 60 total, represent data as reliable and unchangeable as those expressing body weight or basal metabolism. But are they so reliable? A search through the literature showed only one paper on the subject and in this the data were so presented that I could not get the information I wanted.

Accordingly Vanzant and I[2] studied the secretion of two healthy young women daily for a month. In one, who was fairly phlegmatic, the range of free acidity was from 30 to 46 units and the range of total acidity was from 40 to 66 units. The figures tended to follow a curve which apparently corresponded with the menstrual cycle. In this young woman one gastric analysis would be of some value because the variability was sufficiently small.

The other young woman was more temperamental, and when, during the middle of the month of observation, she suffered a severe disappointment, she became much depressed, and coincidentally, the free acidity rose in a few days from a mean of approximately 36 to a high point of 60 units. It then dropped rapidly to 20, and after a swing back to 46 came to rest again about 36 units. The total acidity followed the same course. Obviously, in this woman a single gastric analysis made during the middle of the month would have been almost without value.

Standards of normal acidity at different ages in men and women. The next question was: What is normal acidity, and how does it vary in the

Read before the American College of Physicians, San Francisco, California, April 4, 1932. From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

two sexes and at different ages? In order to answer this question Vanzant and her associates[3] collected data on gastric analysis from 3,746 men and women who were proved to be without organic disease in the digestive tract and otherwise in fair health, and arranged the figures in percentage distribution tables corresponding to five year age groups. Figure 1 shows clearly that gastric acidity rises rapidly during childhood. At puberty the free acid of boys increases faster than does that of girls so that at the age of twenty years the mode or most typical figure for the men is 46 and for the women 31. It is possible that this difference in acidity has something to do with the greater susceptibility of men to ulcer.

The mean and modal acidity of the men falls off with age until finally in the later years of life it coincides with that of the women. The curious feature is that only late in life does the modal or most typical acidity of women fall off, and in them the mean acidity never falls. This makes it seem unlikely that the decline of acidity in men is due to a slow atrophy of the gastric glands because one would expect age to work the same injury to women. Strange to say, Vanzant and her associates[3] found a straight line increase in the incidence of achlorhydria (to the ordinary test meal) with age, in both men and women. In men the percentage varied from 0 at the age of twenty-five years to 23 at sixty years; in women the figures were 3 per cent at twenty years and 28 per cent at sixty years. After the age of sixty-five years the percentage fell off gradually, due perhaps to greater longevity of persons with normal gastric acidity.

A study of the percentage distribution curves of total acidities at different ages showed that they were bimodal; in other words, there were two peaks, one representing the group of persons who have free acidity and the other the group who have none. To the biometrician bimodality always suggests the probability that he is dealing with two different varieties of persons. In this case, one type of man has probably inherited a tendency to develop achlorhydria and the other has inherited a tendency to keep his acid throughout life. The difference may be like that which gives to one man even in youth a shiny bald head and to another a musician's mop which lasts into old age. Using the same simile, the gradual falling off of acidity in older men may correspond to the gradual thinning of the hair with age, a thinning which is usually more marked among men than among women.

A study of the range of gastric acidity in apparently normal persons shows that throughout middle life one can hardly speak of a pathologic subacidity unless the free acid titer is below 20 for men and below 10 for women. One can hardly speak of pathologic hyperacidity unless the titer exceeds 75 units for men and 56 for women.

It would seem also that the physician should be slow to alarm patients over the fact that they have gastric anacidity. He should remember that this peculiarity can be found in one of four apparently normal persons aged sixty years. He may with propriety watch the patient with greater care than he otherwise would, but he

need not give expression to gloomy forebodings.

The age curve of acidity is shifted bodily by disease. Vanzant[4] has shown that with duodenal ulcer the curves representing mean free acidity in men and women are raised about 12 points but otherwise left unchanged. This is a most interesting point, indicating as it does that these curves represent some biologic peculiarity which is too deeply rooted to be altered with ease.

Now that standards of normal are available I believe that the gastroenterologist should give up the old, cumbersome, arbitrary and inadequate classification of data from gastric analysis into acid, subacid, normal, and hyperacid, and substitute the method used by students of basal metabolism. Only as we physicians come to express acidities in terms of a percentage above or below normal can we obtain accurate knowledge in regard to the influence of different diseases and different types of ulcer in gastric secretion. Work along these lines is now being done on a large scale by Vanzant and her associates. It will be reported later.

Studies in regard to pepsin in health and disease. Although much work was done years ago on the amount of pepsin in the gastric juice, it was of doubtful value on account of the crudeness of the technic used. Recent studies with a highly accurate technic[1] have led us to hope that the estimation of pepsin may give to the clinician information of greater value than that obtainable from a study of the acidity. With the method used, the usual value found in normal persons with a fairly calm temperament is about 90 units, whereas the range is from 0 to about 500 units. In persons of an active, nervous, and tense temperament the values range up to 2,000 units. In patients with tractable duodenal ulcer the upper limit is about 800 units, and in patients with intractable duodenal ulcer almost all the readings are very high. It is possible, then, that this test will prove to be useful in helping the physician and the surgeon to recognize early those cases of duodenal ulcer in which treatment of any kind is going to be difficult. A study of the acidity alone is not so helpful because there is not enough difference between the values obtained in persons with tractable and in those with intractable ulcer.

Obviously a study of the gastric ferments cannot be of value in the diagnosis of ulcer because persons with a tense nervous temperament or with pseudo-ulcer commonly have as much pepsin as is found in the gastric juice of patients with an actual lesion in stomach or duodenum.

Summary

Data have been published which throw light on the size of the daily variation in gastric acidity and on the reliability of one gastric analysis. In some persons the variation is so large that little value can be attached to figures obtained from one test meal.

A figure has been published which shows the range and central tendency of measurements of gastric acidity for men and women at five yearly intervals from youth to old age.

The mean acidity of men during middle life is about 15 points higher than that of women. The percentage

of persons with anacidity, after an Ewald test meal, increases steadily from youth to old age. The bimodal distribution curves representing total acidity in the various age groups suggest that there are two varieties of the human race: one with a tendency to maintain free acidity in the stomach, and the other with a tendency to lose it. The range of normal variation is so great that it is only an occasional gastric analysis that can be of any diagnostic value.

The curves representing mean free acidity in men and women from youth to old age are raised about twelve points but otherwise are unchanged by ulceration in the duodenum.

Persons with a nervous temperament commonly have pepsin values from fifteen to twenty times the normal. Similar values were found in most of the patients studied with intractable duodenal ulcer. Patients with tractable ulcer had pepsin values usually less than nine times the normal.

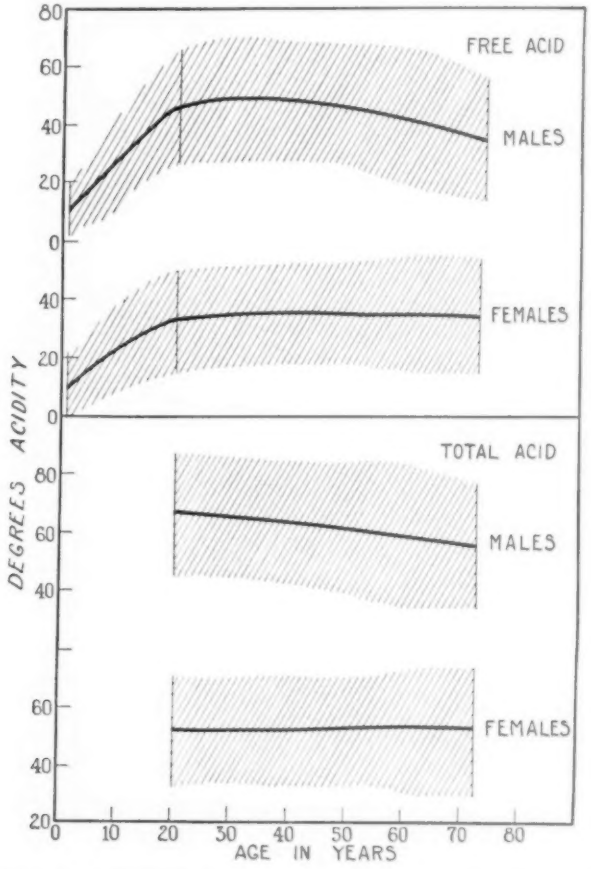

FIG. 1. The range (including 80 per cent of the data), and central tendency of free and total gastric acidity in normal men and women by five year age periods from youth to old age.

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"Medicine" of the American Indian

"THE theologico-physical dualism of the American Indian is best illustrated by his use of the word "Medicine". To the person brought up in the European tradition, medicine connotes some chemical, some regime of life or physical procedure used for its actual alternative effect on the body. To the Indian the term means much more. He may use the word to refer to an herb or drug, but more often it means some supernatural article or agency which may be of aid in curing disease or just as often the same thing may be invoked to insure the success of some individual or tribal undertaking. Anything under the sun might achieve such therapeutic or mystical quality, might become "medicine". Once invoked, the article thus dignified was held to be powerful and sacred. It might be an animal, a bit of wood, a finger from a powerful foe, a spear or a pipe. But once consecrated, it was never harmed if animal, or never again used for lay purposes if it were a utensil. This did not mean that the article was revered in itself as the Indian was always careful to distinguish the fact that its symbolism alone hallowed it. These articles or herbs or even formulae which were supposed to have healing or other benign properties were spoken of as "good medicine", while evil influences or things were referred to as "bad medicine".

From *Medicine Among the American Indians* by Eric Stone. Paul B. Hoeber, Inc., 1932. (See review in this issue.)

Asthenia: Clinical Types and Principles of Therapy

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IN THESE times of stress with life being lived at an ever increasing pace and with financial burdens, familial cares and a multitude of other distressing factors putting a strain on the physical, mental and emotional powers, the subject of asthenia has become an important one. The term "Asthenia", in common with a number of the other terms current in medical parlance, is not used critically but is applied without discrimination to all types of weakness, debility, depression, constitutional inadequacy, or even nervous instability. It is customary to regard as asthenia, the state of weakness manifested in the course of convalescence of most serious illnesses, but in many cases this is simply a condition of general debilitation in accordance with physiological law which will disappear as the organism with the aid of diet and the proper hygiene is able little by little to recover its muscular and nervous force. Certain of the severe infections and intoxications, however, are definitely "dysthenizing" agents and the patients experience a true, pathological asthenia as a complication of their disease. Emotional shocks, worry and prolonged nervous strain are also able to produce asthenia.

The basis of all physiological life is the maintenance of a balance between two or more counteracting forces and as a result there is the equilibrium in endocrine function, in the production of epithelial and connective tissue cells, in vasoconstriction and dilation, acidity and alkalinity, in the heat regulation of the body. The two states of asthenia and hypersthenia seem to be but variations of the normally maintained eusthenic state. Asthenia has been rather aptly styled a diminution of "potential". All energy produced by the metabolism is organized and distributed by the nervous system and just as electrical apparatus may be "geared" at high speed or low speed, human beings may experience an habitually increased influx of nervous force into the muscles and brain and be hypersthenic, or the influx may be less than is the portion of the normal individual and they will be classed as hyposthenic or asthenic. Asthenic individuals may have no discoverable functional disorders and no especial worries or cares, yet they fatigue more easily and rapidly than the normal person while the hypersthenic subject

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may be of ordinary stature, development and function and may even show a low arterial tension, yet he is able to accomplish an enormous amount of work without notable fatigue, due to the tremendous amount of dynamic force which he possesses. A certain degree of asthenia and hypersthenia are exhibited in the course of routine existence and there are variations from day to day in the normal person's dynamic state. Usually this variation is confined within narrow limits but when it passes beyond these limits it becomes abnormal and there may result an asthenia so profound as to resemble stupor or an hypersthenia reaching almost to the point of mania.

The changes in the dynamic state from normal to pathological might be classified as follows:

Hypomania
Exaltation
Hypersthenia
EUSTHENIA
Hyposthenia
Asthenia
Stupor (?)

Asthenia[1-4] is a well-defined state in which there is an insufficient influx of nervous force to support either muscular or intellectual effort, and in which the least movement or expenditure of energy provokes an overwhelming fatigue. Rest and sleep do not alter or improve the condition; diet and medications are of no avail. The asthenia includes both striated and smooth muscle fibers and the digestive system is subject to the same abnormal state of easy exhaustion. There may be slowing of respiration due to asthenia of the diaphragm. Londe[5] finds that there is feebleness of the voice or complete aphony, that the physiognomy becomes dull and the eyeballs sink in the orbits due to insufficiency of the muscle of Müller. There is no dulling or confusion of the mental processes and no loss of perception, although the patient may be unable to read, write, engage in conversation or follow a direct line of thought due to the fatigue which is engendered.

Asthenia is a purely functional state and may even appear without discoverable organic or emotional cause; at autopsy no trace is left on the organism. Benon[6] states that it is remarkable to note the rapidity and completeness with which the asthenia may develop in a few hours or days, its immobility and invariability for an indefinite period of time, and its disappearance as rapid as its installation. It may last but a half-hour or it may become chronic and permanent; the attacks may last for a few months or for a year or two, then disappear and recur at a later date. Where there has been one prolonged attack of asthenia and the patient has returned to a normal state, it may be assumed that there will be a recurrence. Tastevin[7] reports three interesting cases of primary, uncomplicated asthenia, in one of which the condition was permanent and in the other two was recurrent with periods of normal health intervening:

I. The first case was a young man 33 years of age. He had been a lively, active child but at the age of 14 years, when he was a student at the Sorbonne, he felt himself progressively growing weaker following frequent painful headaches and intellectual overwork. For some time he tried to continue his studies but having reached the age of 21 and finding this state persisting he attempted suicide and was interned in an

institution. He left the institution after a time in exactly the same physical state but resigned to his situation. When the case was reported some years later, the patient had been in a state of permanent asthenia for 15 years; all his movements were slow and he became fatigued with the least effort. He described his malady as a feebleness of the nervous system with headache, inertia, lack of energy and decision. It took him two hours to undress himself. When he tried to read, his headache augmented and he was obliged to stop. It was in bed that he was best. His sleep was normal. In the beginning when he was a student, he worried over his condition but now he cared for nothing, he had no interests and merely lived from day to day.

II. A woman, 74 years of age, had been in an institution for eight years following an attempt at suicide in the course of an attack of asthenia. At the age of 24 years, being newly married and pregnant, she had had an attack of asthenia lasting nine months, following numerous difficulties with the parents of her husband. From that time, there had been recurrences almost every year, lasting about six months and coming on at any period of the year. The condition came on almost insensibly and disappeared in about the same manner; within four or five days she found herself ill or cured. During the attacks she remained in her chair inert; she did not wish to talk, would have liked to read but after four or five lines could no longer recall what she had read and after commencing several times put aside her book. She was tormented by her condition; her one fixed idea was her malady. When she was 66 years old, feeling discouraged at having spent her whole life in this way, she tried to jump from a fifth story window, and had been interned in an institution for the eight years following. During the last five or six years there had been no recurrences. During the attacks, this patient had rachialgia and constipation but despite her age, there was no weakening of her intelligence.

III. A woman, 49 years of age, 12 years previously had had an attack of asthenia lasting 18 months. Several years later, there was another attack, and sometime after that a third. Eighteen months after the third attack, she found herself again in this state and feeling it was better to die, tried to take poison and was interned in an institution. She said that at these times she suddenly experienced a powerlessness to act; she wished to do things but had not the force to accomplish what she wished to do. Her appetite was good but it was necessary for someone to feed her. She remained apparently stupified in her chair; reading fatigued her too much and writing was worse. There was a complete lack of ideas and her memory failed her; she responded to questions but liked better not to talk. During the attacks there was no headache but stiffness and constipation existed. She was well for variable periods of time and then this all recommenced; the asthenia disappeared in a few days.

It is notable that in every instance the attempted suicide was not because of any mental aberration but because of anxiety and discouragement over the condition. Tastevin states that the patients may be completely unmoved by what goes on about them, good or bad, but they have an excessive tendency to worry about their own incapacity, which will be manifested according to whether the subject is of an equable, irritable, impatient or anxious temperament.

There are two forms of asthenia, the severe objective form described above and a light, subjective form in which the individuals are able to mask or overcome the asthenia and engage in business or follow a routine of social activity. In the course of general practice in this country, up to the present time, asthenia of the objective type has probably been observed most frequently as a complication of various acute disease states.

For example, in a recently treated case of intercostal neuralgia lasting less than two

weeks, after the pain and other manifestations of the illness had disappeared, the patient found herself in a state of objective asthenia. This extreme weakness was obviously not due to debilitation; the patient and her family believed that she had recovered from her illness yet she was prostrated on the slightest exertion. After an attempt to dress herself or comb her hair, she fell on the bed exhausted and gave up all thought of activity of any sort. The asthenia persisted for about two weeks, then disappeared and the patient returned to her usual routine of household and social duties.

In another case, the patient had acquired a severe streptococcic infection in his hand; with the institution of proper treatment, the infection was controlled fairly promptly but for two or three weeks the least effort provoked an overwhelming fatigue which it was impossible to combat.

The prostration following an attack of grippe is an outstanding example of asthenia. Andrews[8] in an interesting article on grippal infections pleads for more serious consideration of the extreme weakness and cardiac instability following an apparently trivial attack of grippe. He states that he is often consulted by individuals who have not been well since an attack of grippe as long ago as 10 years yet the patients emphasize that they were not critically ill. The following case reported by Benon[9] appears to be an instance of the failure to identify post-grippal asthenia, and the consequences which may be expected if the patients are not kept at repose until the regulating neurosthenic mechanism has righted itself:

This was a man, 31 years old, in whom the asthenia had developed at the age of 12 years and had become chronic and incurable. There was no family history of nervous disease. As a child the patient had had no serious disorders and his physical and mental development were normal. When he was 12 years old, he had an acute illness the exact nature of which is not known; he had a severe cold with fever and cough, remained in bed only a few days and no doctor was called. From that time there had been no infection, intoxication, traumatism or emotional shock, but although he was never really ill, he complained of the most diverse maladies and consulted all the physicians in the neighborhood without obtaining any relief. He was incapable of performing any heavy work or of earning his living although his intelligence was normal. He presented symptoms of *general nervous asthenia*, complaining of fatigue, weakness, headache, backache, gastric pains, diarrhea, constipation, loss of memory, insomnia, numbness and buzzing in the ears. He was unable to read because his vision became cloudy after a short time. He stated that he had not been strong since he was 12 years old and had grown without becoming any stronger.

Perhaps the largest group of patients showing a true objective asthenia which has become permanent are those who have never returned to their normal state after having influenza in 1918. These patients are receiving a great deal of attention at the present time both from the medical profession and the pharmaceutical laboratories, but here also the condition is not recognized as asthenia. The subjects are said to be suffering from constitutional inadequacy, functional depletion of the adrenal mechanism, disturbed thyroids, or chronic invalidism of indefinite origin, and their symptoms are listed as lack of strength, loss of initiative, subnormal temperature, low blood pressure, poor circulatory tone, weak action of the heart, weakness of the voluntary muscles, nervous depression, etc.

Rogoff and Stewart[10] in a study of Addison's disease cite seven cases of adrenal cortex deficiency. The seventh

case in this series seems to be a typical case of post-influenzal asthenia.

This patient after six months in a state of objective asthenia sought hospital care for the persistent weakness and fatigue. Repeated roentgenographic and laboratory examinations were made. He was given dilute hydrochloric acid, iron and arsenic, suprarenal gland and ephedrine but there was no improvement in the condition. With the administration of cortical substance the patient improved but it is possible that the benefit was derived from the systemic effect of the cortical hormone, the most important function of which is to spur oxidation and further metabolism generally, and not to any direct effect on the asthenia.

Asthenia, then, cannot be confused with states of debilitation since profound asthenia may be noted where there is no debilitation and a state of debilitation may exist with no evidence of asthenia. There are certain factors which are able to produce asthenia and which might be called "dysthenizing agents". Intellectual and physical overwork, pain, disturbing emotions, certain fevers, infections and intoxications such as pulmonary tuberculosis, syphilis, typhoid fever, botulism, or malaria, the important events in the sexual cycle, may all be followed by asthenia of variable intensity. Benon[6] states that in the case of severe shock or trauma to any part of the body, if at the time of the shock or wound there has been cerebral disturbance with a total loss of consciousness of short or long duration, the patient is liable to a subsequent chronic asthenia. Yet maladies of the brain, itself, are not necessarily accompanied by asthenia and it is not unusual to see a completely shattered nervous system without a trace of asthenia. In tabes neither the ataxia nor the hypotonia seems to produce asthenia; in Parkinsonism there is asthenia associated with rigidity and hypertonicity. The paralysis which is an almost constant finding in diphtheria has been spoken of as a form of asthenia but here there are definite and well-marked lesions of the spinal cord and peripheral nerves. A natural temporary asthenia is often noted in adolescents during the period of growth.

TABLE I

DYSTHENIZING FACTORS

1. *Pain*
2. *Overwork*
   - physical
   - intellectual
3. *Sunstroke*
4. *Total loss of consciousness*
   - from trauma to head, trunk or members
   - from shock
5. *Strong emotions*
   - anxiety and worry
     - familial
     - financial
   - vexation
   - anger
   - fear
   - jealousy, love, hate
   - religious fanaticism
6. *Neuropathies*
   - nervous affections
   - neuroses
   - psychoses
   - migraine
7. *The important sex epochs*
   - probably the chief physiological factor in contrast to the many pathological factors
   - asthenia may occur during growth
   - hyposthenic and asthenic children may be transformed after puberty[11]
   - diminution or cessation of sexual activity may cause asthenia
     - menopause
     - ablation of ovaries
     - castration
   - asthenia may be noted immediately after pregnancy[12]

8. *Glandular insufficiency or over-activity*
   - exophthalmic goitre
   - Addison's disease (?)
9. *Intoxications*
   - coli-bacillosis (?)
   - alimentary (spoiled meat, poisonous mushrooms, botulism)
   - gases (CO_2, war gas)
   - drugs (sublimate, antimonial tartar, etc.)
10. *Infections (fever in general is accompanied by asthenia)*
    - influenza and grippe
    - typhoid fever
    - puerperal fever
    - malaria
    - tuberculosis
    - syphilis
    - acute articular rheumatism
    - exanthematous typhus
    - cerebro-spinal meningitis
    - epidemic lethargic encephalitis
    - uterine infections
    - dysentery
    - myocarditis
    - chronic focal infections
    - streptococcus infections
11. *Certain anemias and malignancies (?)*
12. *General disturbances of nutrition (?)*
    - pancreatic
      - diabetes
      - hyper- and hypo-glycemia
    - hepatic
      - hepatitis
      - azotemia
      - icterus
      - cholemia
    - renal
      - uremia
      - albuminuria

Asthenia of the subjective type is probably quite common but it may be so vague as to be difficult to distinguish. It may be either constitutional or acquired and like the objective form it may be temporary or chronic. The constitutional asthenic is an individual who does not appear ill; he possesses a certain degree of health but is incapable of augmenting his capital of energy by exercise, diet or hygiene as a normal person may do. These persons spend their lives guarding against fatigue; they recognize their limitations and avoid crowds, exercises and sports, and fatiguing pleasures. An acquired subjective asthenia is most frequent where there is a *chronic infection* or as a *sequela of infection.* There is the same feeling of fatigue and the inability for sustained physical or mental effort but where the condition is permanent, there is a variability in intensity and the individuals are able to mask the asthenia or overcome it by force of their will. Periods of abnormal fatigue and insomnia may occur in the form of attacks with normal periods intervening.

Asthenics are subject to a particular form of insomnia which sedatives or narcotics can rarely overcome; the patients go to sleep readily at 9 or 10 o'clock in the evening but waken at 1 or 2 and remain awake the rest of the night. Headache and eye symptoms, gastric disturbances and constipation are frequent associated findings.

TABLE II

THE ASTHENIC SYNDROME

1. *Muscular asthenia*
   - prostration and general weakness of both the smooth and striated muscles
   - inability to maintain a standing position for a very long time or make physical effort of any sort
   - a feeling of weight or heaviness of the body
   - repose or sleep does not make the fatigue disappear
   - loss of weight
2. *Intellectual asthenia*
   - slowing of the intellectual process and inability for prolonged mental effort

difficulty of remembering and associating ideas because of the effort required
at times a sensation of emptiness in the head
the perceptions remain intact even though the asthenia may be so profound that the patient seems to be in a stupor
the patient has a perfect understanding of his state but cannot overcome it

3. *Emotional tendencies*
muscular and intellectual asthenia may exist independent of all emotion
two classes of individuals probably following their constitutional predisposition
a. the calm resigned type
b. those showing a disposition to "unnerving," irritability, or who feel a constant need to change their location
become sensitive and impressionable, believing that chance remarks or acts are meant to apply to them
show great anxiety over their condition and epigastralgia may follow with a sensation of painful epigastric constriction

4. *Nervous symptoms*
accommodative asthenopia is constant, is increased by work and disappears with repose
headache is very frequent
roaring or buzzing in the ears
dizziness
when head is lowered, when walking or when fatigued
vertigo with a fall is rare if not non-existent
insomnia
is habitual
of a particular type—the patient goes to sleep without difficulty at 9 or 10 but wakens at 1 or 2 and can sleep no more: if he does sleep with the aid of drugs, he is troubled with nightmare and is prostrated on awakening.
may feel a need of sleep during the day, especially when digestion is going on
rachialgia or lumbago
is frequent and at times severe
when localized in lumbar region, subject often believes he has a kidney affection
is increased by work or effort and eased by rest

5. *Visceral asthenia*
a. Gastric asthenia
appetite may be good and food may have natural taste but patient may not have the strength to feed himself
usual alimentation is badly supported
slowness of digestion
post-prandial weight or ballooning
aerophagia is frequent
it may be the gastric symptoms which fix the attention of the patient and cause him to consult the doctor[1]
b. Intestinal asthenia
constipation (may be a week or more between evacuations)
sometimes alternating constipation and diarrhea with mucous stools
c. Cardiac asthenia
manifested more often by tachycardia than by bradycardia
palpitation especially after eating
various disturbances of rhythm
tachycardia is not constant; minor causes, physical or mental, produce an increase in the pulse rate but after 3 or 4 minutes it returns to normal
arterial hypotension is the rule

6. *Genital asthenia is always present*

7. *May be signs of endocrine dysfunction*
thyroid
adrenal

8. *Subjects are sensitive to the action of drugs*
only small doses are needed
condition is aggravated frequently by tonics and stimulants

Hypersthenia

When studying the problem of asthenia, it must be borne in mind that for every degree of asthenia there is a corresponding degree of hypersthenia. There are cases in which, after the return to normal from a state of profound asthenia, the patients find themselves going into a directly opposite state of increasing muscular and intellectual hypersthenia, showing that the normal regulating mechanism has been suppressed. When the hypersthenia and asthenia appear in juxtaposition forming one attack, and are recurrent, the condition is spoken of as a "periodic psychosis," or as "periodic dysthenia" if they appear separately with normal periods intervening. Mania is regarded by some as the highest expression of hypersthenia, but Tastevin states that in these conditions of dysthenia, there may be extreme activity of the faculties with incessant need for movement, but there is no incoherence of ideas as in mania.

He cites the case of a woman, 30 years of age, who for two years had had attacks of "anxiety" coming on at variable intervals and lasting from one-half hour to a month or more. In spite of a total absence of emotional ideas or worries of any kind, during the attacks the patient was in the state of one who feared a calamity. It affected her as a weight on the chest which prevented her from breathing and as a constriction of the stomach. She felt impelled to move about; at night she tossed in her bed and if she slept for a while, she had nightmare. The feeling of anxiety left as suddenly as it came, after which the patient felt relieved but soon found herself in a state of complete asthenia. The duration of the asthenia was in proportion to the duration of the attack; with attacks lasting only a few hours, the asthenia was of short duration. After an attack lasting 1½ months, the asthenia lasted 10 days. But, with attacks lasting over 3 weeks, after remaining prostrated for some days, she spent a short time in a normal state and then experienced a period of exaltation. She explained the sensation as a feeling of well-being, of being happy to live; she woke early in the morning and did not want to go to bed at night. She sang, laughed and thought of nothing but going out. The hypersthenia lasted about 5 days and she then returned to a normal state.

This case is classified as one of the psycho-neuroses, but it is interesting because when an individual wakes in the morning filled with the joy of living, he is inclined to attribute the fact to good digestion or to nicely balanced endocrine function. However, if this same feeling of alacrity and pleasure can exist as a pathological condition, one is forced to conclude that his dynamic state is not so well founded physiologically as might be supposed.

Constitutional Depression

Montassut and Delaville[13] describe as "constitutional depression" a state which is easily recognized as one to which presumably normal individuals are liable, especially those possessing the "artistic temperament". In these subjects there is a daily rhythm of fatigue; the fatigue is original and it is chronic although of variable intensity in the course of existence. The awakening in the morning is difficult; somnolence at this hour is invincible and delays the hour of rising. Muscular activity is almost impossible, mental orientation and verbal expression are difficult, the reactions are pessimistic and there is a feeling of powerlessness and uselessness. With physical exercises or a cold bath the inhibition yields somewhat and as the

morning advances activity becomes easier. Luncheon is generally accompanied by an overpowering tendency to inertia. Toward the end of the afternoon when the normal person is beginning to tire, the fatigue disappears and is replaced by a feeling of animation. This is spoken of as the "5 o'clock cure". The feeling is not one of relief that the day's work is finished, since the same amelioration is noted during periods of vacation and it appears in individuals who do night work. With the "5 o'clock cure" intellectual activity becomes easier and more effective and is accompanied by a feeling of well-being and muscular agility. Dinner brings a temporary feeling of fatigue but this is more easily overcome. It is after dinner and often late into the night that he works with all his ability and with a slight intellectual excitation. The constitutionally depressed subject retires late and usually less fatigued and more optimistic than when he awoke. He realizes perfectly what his sensations will be after an intervening period of inactivity and the routine of fatigue and depression that he must undergo on awakening. This paradox of fatigue appears rather scandalous and the individuals get very little sympathy from their family and associates. One surmises that the old saying,

> "When the sun has gone to rest,
> The lazy man works the best,"

was inspired by the constitutionally depressed.

Warm baths, remaining in an overheated atmosphere, profound sleep, the lounging to which they are prone, and the probable change in body chemistry following the ingestion of food, all aggravate the asthenia. Yet, although it seems necessary to contract a certain amount of physiologic fatigue in order to mask or neutralize the static and essential fatigue, work or effort cannot be pushed beyond a certain limit without producing a state of exhaustion.

Neurasthenia

The most important of "the asthenias" is neurasthenia, or nervous exhaustion. Benon[14] believes that true neurasthenia has a special origin and evolution which distinguishes it from all the other asthenic states, and that this is solely the condition of general nervous exhaustion produced by muscular or intellectual overwork. Overwork is defined as a series of repeated and inadequately repaired fatigues which in time will produce a definite syndrome of the asthenic order. Beard,[15] in 1868, was the first to isolate the condition of nervous exhaustion from the vast collection of neuropathic states and to give to the syndrome the name of neurasthenia. He found that most intellectual families possessed one or more neurasthenic members and that the condition was common among business and professional men, among women struggling to maintain a prominent position in society and among people of all types undergoing prolonged worry or nervous strain. But Beard observed that sunstroke might produce this same state of nervous exhaustion. It is true also that while such diseases as typhoid fever may be followed or complicated by a temporary, objective asthenia, after a very severe case of typhoid fever just as after a severe

surgical operation or a serious obstetrical case, the patient may never be able to recover from the nervous exhaustion but will spend the rest of his days in a state of neurasthenia with the easy fatigability, the various subjective mental and nervous symptoms and the sudden and unexpected giving away of his strength. After a close observation of a large number of cases, Beard listed the symptoms as follows, stressing that no symptom was constant and that only a few or almost all might be found in individual cases:

TABLE III

SYMPTOMS OF NEURASTHENIA

The symptoms may be divided into 3 groups, general symptoms, those which are evidences of cerebral exhaustion (cerebrasthenia) and those which are evidences of exhaustion or irritation of the spinal cord (myelasthenia).

I. *General Symptoms*

1. *A feeling of profound exhaustion*
   - neurasthenics must keep to an ordinary routine as they become quickly wearied with attempting anything new
   - the treacherousness of nervous exhaustion is one of its most constant characteristics; in the morning subject may be able to work, walk or study but suddenly and from no traceable cause all strength may leave

2. *Deficient mental control*
   - inability to concentrate
   - lack of will, courage and self reliance
   - tendency to worry and fret over trifles
   - subject to attacks of mental depression lasting but a short time or for a day or more
   - may be a feeling of hopelessness even in the early and mild stages
   - wrong word slips in ahead of the one intended
   - subject to morbid fears
     - patient may be well aware of his weakness but cannot free himself from these fears
     - may have fear of storms, of going in any one direction, of travelling, of open places or of close and narrow places, a dread of society, of being alone, of responsibility, a dread of being afraid,
     - fear of disease (hypochondria), of dust (will not sit down until chair is well dusted and may get up in the night and dust his clothes)

3. *Insomnia*
   - patient may have no difficulty in going to sleep on retiring but soon wakes and remains awake
   - may be hours before falling asleep, then sleep the rest of the night
   - may sleep fitfully with unpleasant dreams and a painfully active mind
   - may sleep only at night and never by day no matter how wearied
   - may sleep during the day though especially wishing to keep awake and stay awake all night
   - may be subject to drowsiness which does not come to actual sleep; dull, heavy, sleepy without the ability to go to sleep
   - in extremely rare cases, sleep may be normal

4. *Sick headache*

5. *Frequent blushing*
   - a common effect of nervous exhaustion
   - from the slightest physical or mental cause
   - may last months or years and disappear as suddenly as it began

6. *Localized peripheral numbness and hyperesthesia*

7. *Difficulty of swallowing*

8. *Hemi-neurasthenia* (may affect one side of the body more than the other)

9. *Rapid decay and irregularities of the teeth*

10. *Tremulous and variable pulse and palpitation of the heart (irritable heart)*
    - rapidity and quality vary during counting
    - in exceptional cases, pulse is very slow (40 or less)
    - there may be alterations in pulse rate between very high and very low
    - cardiac action is powerfully affected by the mind and under the influence of the emotions
    - pulse is frequently compressible
11. *Nervous dyspepsia*
    - is most commonly found with the nervous diathesis and may be the forerunner of a long list of nervous symptoms through all the organs, the eyes, ears, brain, spine and reproductive system
    - nervous dyspepsia may take the place of many other symptoms, being better when they are worse and worse when they are better.
    - is relieved by remedies with a sedative and tonic effect such as bromides or electricity, without specific reference to the stomach
    - patients have the greatest distress when the stomach is empty and even overeating is a relief
    - mental or physical labor on an empty stomach may cause pain in the eyes, head, stomach or general nervous distress all over the body
    - patients may go for some time on unregulated diet but suddenly ordinary food will cause distress, flatulence, nausea, diarrhea
12. *Special idiosyncrasies in regard to food, medicine and external irritants*
    - patients desire stimulants and narcotics for relief of the exhaustion but one sign of the neurasthenia is the inability to bear even those to which the patients are accustomed (tobacco, coffee, tea, alcohol)
    - some who ordinarily can stand only small amounts of alcohol, when depressed can drink quantities
    - may have an idiosyncrasy for hot or cold water
    - opium is apt to aggravate insomnia

II. *Symptoms of Cerebrasthenia* (indicate that the exhaustion is chiefly cerebral)
- Tenderness of the scalp
- Tenderness of the teeth with whitish appearance of the gums
- Yawning
- Disorders of the special senses
  - changes in "expression" of the eyes
  - pain and aching in the ears due to hyperesthesia of auditory nerve
  - subjective odors and tastes (phosphorus or ozone, bitter and sour)
  - atonic voice (resembles that of deaf person but can be distinguished)
- Deficient thirst and capacity for assimilating fluids
- Congestion of the conjunctiva (neurasthenic asthenopia or irritable eye)
  - the effect of nervous irritation, and comes and goes under exciting causes
  - resembles cold in the eye or the congestion from drinking
  - bad in the morning but disappears at night
- *In cerebrasthenia muscular exercise can be well borne and is frequently desired and sought*

III. *Symptoms of Myelasthenia* (indicate that the spinal cord is chiefly affected)
- Tenderness and pain in any part of the spine from nape of the neck to the tip of the coccyx
- Creeping chills up and down spine
- Convulsive movements of the arm, leg or whole body, especially on falling to sleep
- Fidgetiness
  - one of the myriad results of spinal irritation
  - hand and arm may be so "nervous" patient cannot continue writing
  - when legs are affected, he must get up and walk even though exertion aggravates the asthenia

Dilated pupils
there may be sudden and frequent alterations, or temporary inequalities with one contracted and one dilated
One or both ears, hands or feet may be cold to touch even in warm weather, in a hot room, or when thickly wrapped
Heaviness and stiffness of the muscles
Fleeting neuralgias and shooting pains simulating those of ataxy but probably milder
Vague aching in the loins and limbs simulating rheumatism which may follow over-exertion or come on without apparent cause
Pain in the feet
burning and tenderness at the bottoms of the feet
may be only painful spots
in both neurasthenia and ataxia it comes from the spinal cord but in the latter organic, and in the former functional, disease is signified
in some cases may be reflected from the stomach and genital apparatus
Physical exertion requiring either the upper or lower limbs, especially walking and standing, cannot be borne and if persisted in may aggravate the condition
Symptoms showing exhaustion of the upper part of the spinal cord
pain and heaviness in the back of the head
muscae volitantes or floating specks before the eyes
clamminess of the extremities
general or local itching with no change in appearance of the skin

Neurasthenic patients complain that they have "so many symptoms" but the varying and multitudinous symptoms are largely the result of reflex irritations transmitted not only through the ordinary motor and sensory nerves, but also through the sympathetic system and vasomotor nerves. For this reason neurasthenia must be differentiated from the organic disease which it simulates in many instances, although usually the symptoms of organic disease are fixed and stable while those of neurasthenia appear, disappear and reappear without clear cause.

Ballet[16] states that whatever be the clinical form which neurasthenia assumes, a peculiar mental state always accompanies it. The patient is subject to hypochondria and is haunted with thoughts of cancer of the stomach, softening of the brain, disease of the spinal cord or heart disease, according to the location of his distress. His memory fails him, he is disturbed at the sight of a stranger among his usual associates, is timid, fearful, impressionable and pessimistic. However, the neurasthenic is usually quiet, introspective and retires into himself; he does not show the irritability and egotism which is characteristic of the neurotic. Because of the morbid and introspective state of mind and the complicated reflex action throughout the entire body, innumerable "vicious circles" are established with psychic and physical disorders acting and reacting one on the other.[17] The subjects may be fat, hearty and even vigorous looking men who deplore the complete change which has taken place in their personality, the fears and obsessions, the digestive and circulatory derangements, the weakness of will and overwhelming lassitude which all unite to give them a feeling of impotence (Ballet). Beard reports the case of a clergyman of middle age who had suffered from neurasthenia for many years following heat prostration. Among numerous other symptoms were attacks of depression lasting about a day and brought on by any exhausting or disturbing influence. The attacks were usually ushered in

by a feeling of mental exaltation, followed by diplopia and a regular series of minor nervous phenomena.

The asthenia of neurasthenia is usually subjective and often presents the peculiarity of localizing in a certain muscular group. Where there is spinal exhaustion and the asthenia is confined to the lower extremities, the patients, usually neurasthenic women, finding they are unable to walk or even to stand believe they are paralyzed and refuse to leave their bed or couch. These individuals may unnecessarily remain helpless invalids for the rest of their lives. Only about 50 per cent of the cases of neurasthenia are cured.

With reference to a constitutional neurasthenia, Ballet believes that where there is an inherited nervous weakness of infectious or other origin, or a neuro-arthritic constitution, the subjects are on the verge of neurasthenia from birth since their nervous system tires even in the course of a regular and quiet life. Londe finds that in such cases there is a failure to adapt the psychic to the somatic life, or a failure to adapt the individual to the exterior world, to his social milieu, to his occupations. However, cases of true neurasthenia among this group of subjects are probably rare.

Psychasthenia

Often, after the development of a well-marked neurasthenia, new and more serious troubles of a psychopathic order will manifest themselves. Aschaffenberg[18] finds that the stronger the body, the more clearly the clinical picture of neurasthenia will appear, and the more serious and continuous the damaging influences the more severe will be the exhaustion of the forces, but, even so, in such cases the neurasthenia does not progress beyond itself and the organism remains free from the many and varied psychopathic complications which may develop in a weaker subject or where the nervous diathesis predominates. In such cases, neurasthenia may be but the forerunner of insanity, in the form of melancholia. Hysteria is rare although some hysterical symptoms may be present. Benon lists the possible psychic sequelae of neurasthenia as follows:

- A disposition to anger, unnerving and irritability
- Mental confusion (confusion, usually transitory, in perceptions with no recognition of persons, places or things)
- The obsession phobias
- Alcoholism
- Amnesia
- Hypochondria
- Periodic psychosis
- Mania
- Various forms of delirium (persecution, etc.)
- Melancholia
- Dementia praecox (in young subjects)

Aschaffenberg defines the psychasthenic states as the *slight* forms of psychic disorder which belong to the borderland between mental health and disease; the patients are neither insane nor quite sane.[19-23] Janet[24] has collected and grouped under the heading of psychasthenia all the functional psychological states, the absurd fixed ideas, the useless and ridiculous manias and unjustified fears and obsessions, which appear and disappear in the form of attacks or crises with

more or less normal periods intervening. Janet believes that such mental troubles have a relationship to the regularity of intracephalic pressure and vasomotor troubles, to digestive disorders from gastrointestinal atony, to urinary hypoacidity, cardiac weakness and vascular hypotension, to troubles of the secretions and of genital function.

Burr[25] considered that the term "psychasthenia" should be reserved for the state of pure mental exhaustion from intellectual overwork and excessive nervous strain (cerebrasthenia) and that neurasthenia is the more or less constitutional state described above by Ballet and Londe.

Neurocirculatory Asthenia

The condition variously known as neurocirculatory asthenia,[26-28] neurocirculatory myasthenia,[29] effort syndrome,[30] irritable heart,[31] soldier's heart, disordered action of the heart,[32] etc., has been brought to the attention of the medical profession during the different wars in this country and in Europe when the excitement, fear and emotional strain of examination for the army or the exertion of actual service have made active an often latent instability or weakness, which is evidenced principally by disordered heart action. The heart, itself, shows no lesion either of the muscle or of the valves, and patients with true heart disease do not present the syndrome. The symptoms of neurocirculatory asthenia may be listed as follows, stressing again that the symptoms vary in prominence and are not all present in the same individual:

TABLE IV

Symptoms of Neurocirculatory Asthenia

1. Easy fatigue and lassitude
2. Disordered heart action
   - tachycardia
   - forcible beating
   - palpitation
   - arrhythmias
   - systolic apical murmur in 85 per cent
3. High systolic pressure
   - after exercise the systolic pressure rises and the diastolic pressure may drop to zero (Robey and Boas)
4. Left chest pain and soreness of the skin over the left chest
5. Defective capillary circulation
6. Cyanosis of the hands and lips
7. Breathlessness on exertion
   - may be due to
     - (a) reduced vital capacity of the lungs
     - (b) irritable nervous system
     - (c) acid reaction of the blood
       - With the addition of only small quantities of CO_2 or lactic acid produced by exertion, the blood due to a deficiency of certain blood constituents becomes more acid than normal and this is immediately signaled by breathlessness, the respiratory center being extraordinarily sensitive to the blood reaction (Lewis).
8. Giddiness, dizziness on lowering the head, or vertigo
9. Fainting with or without loss of consciousness
10. Sweating
    - It is common to see these patients shaking with cold and perspiring profusely from the armpits
11. Increased susceptibility to cold and changes in the weather
12. Exaggerated reflexes
13. Tremor
14. Headache
15. Blushing and pallor
16. Irritability of temper
17. Inability to fix attention
18. Sleeplessness or disturbed sleep with bad dreams
19. Aphony

Examination of these patients has shown that in at least 50 per cent there is physical weakness and an inherent nervous instability, for which there is no cure; in the army they are classed as a group of "substandard" men and in civil life they represent the various constitutionally inferior individuals usually with family histories of neurotic and psychopathic disorders. Where the condition was not constitutional, it was found to be due to the too-severe drilling and the hardships of army life, or to be of infectious origin. Many of the subjects showed evidences of a low-grade infection from diseased tonsils and teeth, intestinal infections, incipient or healing tuberculosis, etc., or the symptoms might have dated from an acute infection such as rheumatism, typhoid, dysentery, pneumonia, malaria. Where the condition was attributed to the rigors of war and army life, no definite constitutional weakness could be determined but the individuals had been recruited from clerks and office workers, students, waiters, etc., and could not adapt themselves to the new environment.

Lewis explains that when a healthy man takes sufficiently strenuous and prolonged exercise, he experiences a certain well-defined set of symptoms, such as breathlessness increasing in intensity, consciousness of the heart action with elevation of the pulse rate, giddiness or faintness, fatigue, aching over the precordial region and later more violent and widespread pain, and finally exhaustion, and the only difference between this physiological state and the condition known as neurocirculatory asthenia is merely that in the latter a much smaller amount of effort is required to produce the syndrome.

It would be our opinion that here there is no trace of asthenia but rather an extreme instability of the sympathetic nervous system. Rothschild emphasizes that neurocirculatory asthenia cannot be regarded as a disease entity and that "the name is purely descriptive of the major symptoms, which are referable to the nervous and circulatory systems and associated with an increased susceptibility to fatigue." Crile[33] in a recent paper states that in making a diagnosis, all the cases of mental or psychic origin and all those in which there is infection or a heart lesion should be ruled out, and then if, in the absence of all these, there is extreme cardiac instability, if the pupils dilate as the result of pressure on the epigastrium, if tremors, sweating and cold hands and feet are present, a diagnosis of neurocirculatory asthenia may safely be made. He believes this is a pathological state in which there is an excessive stimulation of the adrenal-sympathetic system and advocates denervation of the glands as a remedy. Simici, Popesco and Sandulesco[34] concluded that in many of the cases of permanent cardiac instability there is a latent hyperthyroidism.

Hyposthenia

Mercier[35] describes hyposthenia as a state intermediary between "normal" and a complete, well-characterized asthenia. The "hyposthenics" are the patients who are always in a state ot hypovitality, who fatigue easily and rapidly, who have no courage, no interests, no amusements. Their diges-

tion is poor, they sleep badly. On examination, no determining affection can be found but they show muscular hypotony and visceroptosis, hypocombustion with a decreased basal metabolic rate, hypothermia and arterial hypotension. The hyposthenic syndrome might be described as general hypofunction; the organism is regulated at a point "between physiology and pathology" and it is difficult to decide where the deficiency commences.

Very often these individuals are tall and spare with sagging abdominal viscera, low resistance and a caliber of mind which makes them unacceptable as companions, and it is this type which is usually thought of as the "hyposthenic habitus". However, there are many tall, spare persons with elongated and ptotic viscera who have good digestion, a healthy mental outlook, emotional stability and a fund of nervous energy beyond the normal. Also, Ballet describes a "precocious neurasthenia", which makes its appearance at puberty or a little later, and is found in patients who are notably taller than the average and whose girth of chest and volume of muscles are not proportionate to their height. These *neurasthenics* are almost always of the male sex, they are long and lean, and their nervous system is endowed with excessive fragility and yields to the slightest shock.

This exaggerated growth of the long bones at puberty is one of the most pronounced manifestations of thyroid over-activity and since a fairly large percentage of these patients show signs of thyroid dysfunction, it is a question whether some are not suffering from hyperthyroidism rather than from either asthenia or any fundamental nervous trouble. In normal individuals of the same body type, it might be supposed that the thyroid had quickly returned to normal function.

The two terms, hyposthenia and neurasthenia, have come to have a very broad meaning and are used to describe almost any kind of constitutionally inadequate or neurotic individuals[36-39]. There is a nondescript group of patients who are passed around from physician to physician and on to surgeons and various specialists. By the time they are finished, they have had their appendices and gallbladders removed, have had a partial or total thyroidectomy, have probably been to a sanatorium for treatment of tuberculosis or have had treatment for peptic ulcer. No therapeutic measure seems to be of avail and the patients after years of treatment are classed as either hyposthenics or neurasthenics, depending upon the mental attitude, and, one hopes, are given a logical treatment of support and encouragement. Every clinic has its quota of these cases and the physician does well if he can avoid adding to the patient's distress.

It seems that most of these patients are not necessarily asthenic or neurasthenic but are what Kerley speaks of as "50 and 75 per cent individuals"; they are never able to adapt themselves to their environment and are never equal to what is required of a normal person. The histories in these cases show, for instance, that the father died at 47 of pulmonary tuberculosis, the mother died at 60 of Bright's disease and four sisters and brothers died in infancy. Deschamps remarks that every infant is born with a certain amount of "initial force" which remains the distinctive mark of the individual; it is

his biological destiny. It is probably because the terms hyposthenia and neurasthenia are used so indiscriminately that the real condition of asthenia is so little recognized.

Etiology

Deschamps[40] states that the sthenogenic function comprehends two principal factors: The production and the distribution of energy. Energy is furnished by the metabolism and the secretions, and the nervous system has the function of organizing the use of the force created by favoring or inhibiting its distribution. The fact that, on the basis of exactly the same physiological state, voluntary and involuntary movements and ideation may vary in rapidity, force and duration, would seem to imply a variability in the transmission of energy. The degree of asthenia or hypersthenia might be referred to as the neurosthenic state, in contrast to the state of physical strength depending upon size and development, nutrition, hygiene, etc. Tastevin says that the organism is dependent upon this neurosthenic function for the power to execute any voluntary movement or for the power to think. The will, the perceptions and the special senses remain intact, but the asthenic lacks the actual power to think or to act so there must be an inhibition somewhere between the ideation and the transmission of the nervous influx which is necessary for the production of muscular contractions or to assemble ideas. In hypersthenia the influx is excessive; ideation is quick and lively with a facility of expression; the individual has a feeling of confidence and self reliance; also, there is a desire for muscular activity and all movements are executed with ease and rapidity. Since the nerve centers are the accumulators, transformers and distributors of all energy produced by the unceasing process of metabolism, it follows that in asthenia it is the nerve centers which are deficient.

It has been suggested that anything which precipitates a disturbance of sympathetic function will cause asthenia. The sympathetic system is responsible for automatic or involuntary movements; it is the system which innervates the smooth muscles and the glands. Cannon[41,42] states that the neurone relations seem devised for widespread diffusion of nervous impulses; the extensiveness of the distribution of the fibers is one of the most prominent characteristics of the sympathetic, in contrast to the parasympathetic, division of the vegetative system. Also, the connection of single preganglionic fibers with numerous outlying neurones does not seem to be arranged for specific effects in this or that particular region. The sympathetic is in close relation with the cardiovascular, the digestive, and genito-urinary systems. The muscles of respiration are striated muscles and have no connection with the sympathetic but those surrounding the bronchioles are smooth and are subject to vegetative control. The fibers concerned in the maintenance of arterial pressure, the heart rate, the size of the pupil, etc. are constantly discharging while others such as those leading to the sweat glands are normally at rest; all parts are capable of reflex excitation and inhibition (Bard).

The results of excitation of the two divisions of the vegetative system might be listed as follows:

TABLE V

VAGOTONIA	SYMPATHETICOTONIA
myosis and ciliary contraction	dilation of the pupils
increased secretion of saliva	exophthalmia
contraction of bronchioles	dilation of bronchioles
bradycardia	tachycardia
hyper- and at times retro-peristalsis	inhibition of peristaltic movements
gastric hypermotility and hypersecretion	inhibition of gastric secretion
vomiting	relaxation of stomach and intestines
constipation	diarrhea
bladder evacuation	bladder retention
	extreme weakness
	tremors in the skeletal muscles
	syncope
	"goose-flesh"
	erection of hair
	hyperhidrosis:
	from forehead
	from axilla
	from palms and plantar surfaces
	constriction of the arteries:
	pallor
	cold extremities
	various ischemias
	liberation of sugar from the liver
may be sequence of acidosis, elevation of vagal tonus and vaso-dilation	may be sequence of alkalosis, elevation of sympathetic tonus and vaso-constriction
high blood potassium	high blood calcium
high blood phosphorus	low blood phosphorus
vagotonia increased by pilocarpine	sympathicotonia increased by adrenalin
vagotonia decreased by atropine	

When the sympathetic division of the vegetative system is unduly excited, a definite set of symptoms will be produced, chief among which are *weakness* with a loss of the feeling of stability and possibly tremulousness, tachycardia, sweating, diarrhea, and vascular contractions causing pallor or localized ischemias.

In the nervous hierarchy, the sympathetic is regarded as the connecting link by which cerebral activities act on the viscera. Bard[43] believes that the marked tendency of the sympathetic to react vigorously and as a whole under conditions of stress implies control of the system by a central mechanism. Also, all sympathetic discharges can be broken by central inhibition or augmented by central excitation.

The vasomotor center is situated in the bulb. Bard states it is certain that a narrowly localized bulbar mechanism makes a definite connection with the sympathetic outflow to the arterioles. Experimental work indicates that there is a single cardiac center in the bulb, controlling and coordinating vagal and sympathetic discharges to the heart. The vasoconstrictor, vasodilator, cardioaccelerator, and cardioinhibitory mechanisms are closely related physiologically and anatomically they appear

to be closely juxtaposed in the medulla oblongata. Deschamps states that the bulb has been proven to be the most sensitive and easily affected of the nervous centers and that asthenia is especially a bulbar state. In asthenia and in neurasthenia, there may be constant alternating of vascular contraction and dilation and extreme instability of the pulse with variations of cardiac rhythm merely on moving. A low blood pressure is a constant finding in asthenia but it is also common in hypersthenia. We have observed one of the most truly hypersthenic normal individuals that could be found whose systolic pressure during the most active period of his career was consistently around 100.

Bard finds, however, that there is no indication of a localized bulbar center for such sympathetic processes as the secretion of sweat, the erection of hair, inhibition of gastrointestinal motility and dilation of the pupils.

In the organization of the central nervous system, each of the lower mechanisms is influenced or controlled from above; the higher levels may not be necessary for their function but they are able to influence it. Superimposed on the bulbospinal mechanisms controlling the sympathetic is a mechanism located at the base of the diencephalon which is capable of causing a simultaneous discharge over the entire sympathetic system and which is activated in times of stress and emergency (Bard). Huber and Crosby[44] state that the diencephalon is a primary center involved in various types of emotional expression. The diencephalon is divided into the hypothalamus, the epithalamus, and the dorsal and ventral thalamus. Various researches indicate that the thalamus is closely linked with the whole range of pleasurable and painful qualities; irritation or injury of the region may change the whole affective attitude of a person. Pain apparently comes into consciousness in the thalamus. The diencephalon also appears to contain the neural mechanism essential for the maintenance of body temperature and it is significant that exposure to cold and strong emotional excitement call forth similar bodily changes by activation of the sympathetic through stimulation of the diencephalon. Pain and disturbing emotions are two of the most important of the dysthenizing factors. Also hypothermia and increased susceptibility to cold are common findings in asthenia and changes in the affective attitude of the subjects are frequent. There is much to suggest that it may be in the diencephalon that the mechanism regulating the neurosthenic function is situated.

Londe finds that among maladies of the nervous system it is those of the cerebellum which are most often accompanied by asthenia and he believes that asthenia is a cerebellar-sympathetic phenomenon.

Danielopolu[45], after 20 years' research, states that the vegetative system possesses an automatic tone which is maintained by the action of the electrolytes, the secretions and the various substances produced by the vegetative organs themselves. Normally these are furnished in such proportions that there results an ideal milieu for the maintenance of functional equilibrium with the two physiologically antagonistic groups, the sympathetic and para-

sympathetic, in a state of permanent and equal excitation. But over the whole system reign the encephalic coordinating centers and the cerebral cortex, which has an incontestable influence on the organs with vegetative innervation. The cardinal factor in asthenia is the actual inhibition of nervous influx necessary for voluntary movements and for the process of thought; in hypersthenia the ease and rapidity of all voluntary movements and the quick ideation are the predominant characteristics. It might be logical to suppose, therefore, that the dynamic state is controlled at the highest level with various reflex influences on the lower mechanisms, but the reflex action between the different regions is so strong that it is difficult to determine just where the inhibition occurs.

Regarding the constitutional states, Pende[46], Garrod[47], Draper[48], *et al.*, like to speak of asthenic, hyposthenic and hypersthenic types which seem to have reference mostly to the endocrine glands and to embryonic development. The asthenic type is supposed to result from such factors as an overdeveloped lymph system, too much stroma for the parenchyma, or defects in the chromosomes; Deschamps believes that what is transmitted is a defective structure of the protoplasm and a certain physicochemical aptitude. However, there are all sorts of constitutional deficiencies and it would seem that a condition could be regarded as constitutional asthenia only when the deficiency is in the nerve center responsible for regulating the neurosthenic state. Londe states that when the asthenia is constitutional it may manifest itself from birth in the slowness and rarity of the child's movements, the difficulty even of swallowing and in the cry. Since clinical study fails to associate the asthenia with any cause whatever, it must be congenital.

Differential Diagnosis

The condition of asthenia is to be distinguished from such states as atony, apathy, lethargy or melancholia.

Asthenia is a *dynamic* state; atony, or the abolition of muscular tone, is a *static* state of the muscles. The sthenia or dynamism is the active phenomenon of the sthenogenic function and the tonus is the passive or automatic phenomenon. Muscular tone, which is not the same as the reflex, is a state of automatic contractility, a state of tension (Deschamps). There may be atony due to lack of exercise, to stretching and sagging of the visceral ligaments and muscles with a consequent elongation and ptosis of the organs, or after pregnancy with the relaxation and loss of tone of the entire abdominal musculature. This state of atony, however, need not be accompanied by any degree of asthenia.

Tastevin explains that apathy is a state of *activity* which is generally constitutional and in some respects resembles asthenia. When the apathetics speak, their voice is slow and relatively low; their gestures are slow. Their motive reactions of emotional origin are restrained; where a normal person will laugh, the apathetic will smile. Apathy differs from asthenia in the fundamental respect that while the asthenic is rapidly exhausted when he moves, the apathetic can accomplish as intense and as prolonged move-

ments as a normal person. On the one hand, it is a question of the supply of nervous matter, and the influx is soon exhausted; on the other hand, because of a constitutional nervous disposition, the expenditure is made slowly but may be long continued.

It might be said that some of the toxemias and metabolic states produce lethargy rather than asthenia.

Objective asthenia, especially where the patient has become depressed over his inability to regain his normal state, is often wrongly diagnosed as melancholia but melancholia is a distinct and well-defined mental disorder. In the second case described by Tastevin, the patient had been subject to attacks of asthenia lasting 6 to 9 months for over 40 years and at the age of 74, there was no weakening of her intelligence. Yet melancholia may be complicated by asthenia, and asthenia occurring in a weak organism may develop into melancholia.

In table I is given a list of the conditions and states which the various authors believe can produce asthenia. However, as Londe states, almost any lesion or even a slight and localized functional trouble may diminish muscular energy, and it is necessary to distinguish between those causing a true asthenia, those which by disturbing the metabolic processes produce a state of lethargy, and those which disturb the equilibrium of the vegetative nervous system. The problem is a complex one and the intricacy of body structure and function and the innumerable possible complications of disease make it difficult at times to decide just what is asthenia and what is not. For instance, included in the list are hypoglycemia and diabetes. Hypoglycemia may be due to hepatic disorders, to hyperthyroidism, to hyperinsulinism from various causes, but among the most notable symptoms of hypoglycemia are mental confusion, epileptiform attacks, stupor, mania, etc. The manifestations of a moderate lowering of the blood sugar level are[49–54]:

weakness
fatigability
pallor
sweating
restlessness
rapid pulse
muscular twitching
dilation of pupils
disturbed sleep
anxiety
ravenous hunger

Cannon, McIver and Bliss[55] explain that it is the sympathetic fibers which release glycogen from the liver and this reaction of sympathetic excitation is due to increased adrenal discharge in response to nervous impulses and is another remarkable example of automatic adjustments within the organism when there is a disturbance endangering its equilibrium. The mechanism protecting the body from hypoglycemia probably operates in two stages: A primary stage in which sympathetic activity with adrenal secretion occurs to mobilize sugar from the liver, and, if this proves inadequate, a secondary stage in which the activities of the first stage are intensified and augmented in convulsive seizures.

Diabetics complain of both weakness and depression yet the weakness may well be due to the inadequate diet or to the reaction of the sympathetic system to the hyperglycemia and the depression may be the result of a collec-

tion of partly metabolized products which will lead eventually to acidosis and coma. However, it is claimed, also, that the auto-intoxication of diabetes may act as a dysthenizing agent, in which case the asthenia should be distinguished from the other forms of weakness occurring during the course of the disease from other causes.

Colibacillosis is mentioned as a dysthenizing agent but Goiffon[56] has found cases where the colibacillosis as well as the asthenia (?) seemed to be the result of an underlying alkalosis.

Many authors believe that it is disturbances of the acid-base equilibrium acting on the vegetative system which causes asthenia, although there seems to be some confusion as to whether a predominating acidity or alkalinity causes vagotonia or sympathetico-tonia[57-60]. Goiffon finds that, in reality, alkalosis and acidosis are but two deviations of the normal equilibrium which, after reaching a certain point, produce analogous troubles. He believes, however, that the rôle of alkalosis in pathology is vast and lists the general findings about as follows:

TABLE VI

ALKALOSIS

lassitude (is common)
muscular weakness
drowsiness
loss of memory
headache with a tendency to vertigo
tachycardia
low arterial pressure
respiration is either slow or superficial, ventilation is diminished, and the pressure of carbonic acid is raised
digestive troubles are constant
hepatic insufficiency is very frequent
constipation with or without attacks of diarrhea
sometimes there exists a diarrhea of fermentation with very acid stools and a relatively low level of total organic acids
urinary organic acids may reach three or four times the normal when the urine becomes alkaline, showing imperfect combustions
blood uric acid, lactic acid and oxalic acid are augmented
phosphaturia and alkalosis are almost always associated
a vegetable diet aggravates the condition by further alkalinizing the blood

Drouet[61] in a discussion of the relation between the acid-base equilibrium and the equilibrium of the vegetative system, states that "anxiety" has long been catalogued as a manifestation of sympatheticotonia and that the individuals show a permanent ionic alkalosis and a permanent hypoacidity of the urine, increased during the attacks. Guillaume (cited by Drouet) calls "anxiety" the morbid psychic tendency toward which the sympatheticotonic inclines. Drouet states also that in epileptics there exists an habitual alkalosis even reaching a blood pH of 7.70; the number and intensity of the crises seem to vary with the alkalosis and in the intervals between the attacks the pH returns to normal. He cites Walther and Guillaume as having demonstrated that an epileptiform attack is the consequence of encephalic ischemia due to an energetic constriction of the arteries of the brain, that is, to a vascular sympatheticotonia which extends also to the arteries of the cutaneous tissue causing pallor and to every arterial tree causing an elevation of the arterial tension before an attack and at its beginning. He believes that ophthalmic migraine is characterized by

sympatheticotonia in the form of arterial spasm and by blood alkalosis.

Montassut and Delaville believe that the "constitutionally depressed" have a tendency toward a chronic alkalosis and that the inhibitions to which they are subject yield only after a certain amount of muscular activity has caused acidifying of the blood. Goiffon believes that the type of individual described above as the "hyposthenic" is really possessed of an alkaline diathesis or a predisposition to a permanent and constant alkalosis. Meyer[62] believes that an abnormal alkalinity of the blood serum is the *primary* lesion in cancer which, in conjunction with certain other factors, favors the appearance of the cancer wherever a chronic local irritation is present. He reports cases of inoperable malignant tumor with metastases which were, to all appearances, cured by inducing acidosis and by keeping the pH at the normal level with hydrochloric acid and inhalations of O_2-CO_2 whenever a recurrence seemed likely.

The investigators who are interested in hypoglycemia say this is a very common finding and that wherever there is a state of notable weakness and easy fatigability a low blood sugar should be suspected. Those interested in alkalosis believe that in all states of slowed up energy, the trouble may be attributed to alkalosis. Likewise, those studying the rôle of the adrenals in the body economy, state that asthenia is the result of depleted function of the adrenal cortex. It is assumed that Crile's theory of adrenal-sympathetic overactivity as the cause of neurocirculatory asthenia refers to the adrenal medulla and an increased secretion of adrenalin. But in Addison's disease, due to cortical deficiency, an entirely different state is produced which is also spoken of as asthenia.

TABLE VII

ADRENAL CORTEX DEFICIENCY

- general languor and weakness (asthenia is the cardinal symptom)
- low blood pressure
- pigmentation of the skin due to abnormal deposits of melanin, the normal cutaneous pigment
- gastrointestinal disturbances of varying severity
  - vomiting is constant and sometimes uncontrollable
  - anorexia
  - nausea
  - aversion to fat
  - constipation
  - acute gastric ulcers
- epigastric pain
- abdominal wall may be rigid and tender simulating peritonitis
- loss of weight but it is noted that in a large percentage of cases the patients are overweight at the time of the first symptoms
- weak heart action
- vertigo and faintness on arising from bed
- hypothermia or fever
- nervous symptoms are numerous and prominent
  - mental irritability
  - restlessness
  - areas of hyperesthesia
  - hallucinations
  - actual delirium and even acute mania
  - convulsions
  - coma
  - nervous symptoms may be due to either anoxemia or to degenerative changes in the central nervous system
- cortical deficiency is caused by two principal pathological lesions, tuberculosis and simple atrophy; pigmentation is more often associated with atrophy.

In this syndrome there are very few of the sympathetic symptoms which are so prominent in neurocirculatory asthe-

nia and in hypoglycemia while the vomiting suggests vagal predominance. The two significant findings from the standpoint of asthenia are the fatigue and the low blood pressure. Yet almost without exception, by the time these symptoms appear the adrenal tissue, of both medulla and cortex, has so degenerated that the patient survives only a few months at the most, while asthenia even of the objective type may exist for years and it is specifically stated that at autopsy no trace is left on the organism. In Addison's disease degenerative changes in the central nervous system are often noted in addition to those in the adrenal glands. Rogoff and Stewart[10,63] believe that the low blood pressure in Addison's disease is probably a manifestation of intoxication. Rowntree[64] also states that there is much about the terminal picture in Addison's disease to suggest intoxication, affecting chiefly the central nervous system. Certain signs of intoxication were apparent in a series of seven cases reported by Hartman and his associates[65]; laboratory examination showed a blood urea extending from 33 to 130 milligrams in five of the seven cases, and in two there was a leukocytosis of 14,000 and 21,600 respectively. The basal metabolic rate showed from 9 to 28 per cent decrease.

If it be true that the adrenal cortex is largely concerned in the destruction of products of metabolism and bacterial toxins and in furthering oxidation generally, any symptoms of intoxication following cortical deficiency are easily understood. But the point of interest in this discussion is whether this is a state of intoxication which is to be differentiated from asthenia or whether the intoxication acts as one of the dysthenizing agents. In this connection, reference might be made to an article by Porritt[66] describing a type of lead poisoning in which the usual symptoms of plumbism are not exhibited. In these cases there is a slow, insidious saturation of the system over a long period of time by infinitesimal doses of lead contained, usually, in drinking water which is piped through lead pipes. The chief complaint of these patients is that they are "always tired". Porritt states that a strange *lethargy* creeps over the sufferer; he loses interest in life and feels a "weariness of flesh and brain". As the condition progresses, he becomes gloomy and taciturn; instead of joining in conversation with relatives and friends he sits silent and apathetic as if overcome by thoughts too melancholy to utter. His bowels are constipated and stubborn, he derives no satisfaction from his food and perhaps has abdominal discomfort which he puts down to indigestion. Sleep brings welcome respite but he gets up tired and weary in the morning. In neurotic females, emotional outbursts with flatulency and abdominal pain, may punctuate the melancholy. Lead is quickly excreted and the symptoms disappear when the cause has been removed.

The author states that in such cases the subject prefers sitting by the fire to making an effort of any sort yet when he forces himself through his tasks he finds no diminution of brain or bodily power. Feinblatt[67] in reporting a case of Addison's disease fol-

lowing tuberculosis of the vertebrae states that though the symptomatic asthenia was great, the power of the voluntary muscles to do work was normal. Cancer is mentioned in the table as one of the dysthenizing factors, but since all cancers do not cause asthenia it may be that it is the type of malignancy developing in a medium of chronic alkalosis which causes, not asthenia, but a similar state of intoxication. Such conditions not only poison the whole nervous system but in addition alter the internal chemistry and even the structure of the protoplasm of the cells.

Deschamps explains that there are three distinct conditions: (1) *Fatigue* which is the result of actual tiring; (2) *fatigability* which is anterior to fatigue and is a lowered work-tolerance; and (3) a *sensation of fatigue* which may exist independent of both fatigue and fatigability. A subject may be asthenic without experiencing the sensation of fatigue if he does not expend his capital of energy or he may experience the sensation of fatigue without being either fatigued or asthenic.

The numerous individuals who are called "lazy" undoubtedly experience the sensation of fatigue. Fuller[68] remarks that activity creates the capacity for further activity and that laziness is a purely mental condition with material physical consequences. It is the rapid distribution of oxygen to the tissues which constitutes healthy organic life. In anemia, where the reduced oxygen supply to the tissues is due to the diminished hemoglobin or erythrocyte count, a "lack of force" is also noted.

TABLE VIII

ANEMIA

easy fatigue and general lack of physical energy
inability to stand prolonged mental and physical strain
patients are never very ill and never very well
they become breathless on the slightest exertion
are nervous and worry over trifles
there is impaired nutrition and weakened action of the heart muscle
cold, and perhaps moist and clammy, hands and feet
a tendency to chilblains
gastritis is common in all forms of anemia and, in the extreme type, gastric ulcer
there is a lowered resistance to even ordinary infections

All infections and intoxications may cause either anemia[69] or the syndrome of sympathetic instability so in the presence of an infective process, it will be a question of differentiating these two forms of weakness from asthenia.

If one wishes to assume that all conditions causing a lack of force or strength should be considered "asthenia" the problem might be solved by stating, as does Deschamps, that there are asthenias of production and asthenias of distribution. The asthenias of production would include all the states of weakness, fatigue, depression and lowered resistance caused by the various physicochemical disturbances, glandular disorders, malnutrition, anemia, toxi-infections or any other factors which interfere with metabolism and the production of energy. Asthenias of production would include also all the constitutional states, the 50 and 75 per cent individuals, where the organism is not equipped to produce sufficient energy.

The same author uses a slightly different classification as follows:

Asthenias of insufficiency where there is an inadequate supply of energy produced
Asthenias of exhaustion where the supply has been exhausted as in convalescence or perhaps in neurasthenia
Asthenias of inhibition where there is an obstacle in the nervous system which prevents the transmission of energy

Deschamps states, however, that to call every diminution of energy "asthenia" is a misinterpretation and most of the other authors agree that asthenia is strictly autonomous and that the term should be confined to the "asthenias of inhibition" where there is an arrest of the transmission of energy.

Treatment

Except in the constitutional cases, asthenia occurring in the absence of a definite dysthenizing agent is probably rare. Asthenia is an effect rather than a cause. Benon finds that asthenia complicates a great number of disease states, that ordinarily it is of neither diagnostic nor therapeutic interest and when the dysthenizing cause has disappeared the neurosthenic equilibrium will right itself. Deschamps says that the most curious symptomatic consequence of all types of asthenia is the impossibility for the patient to accumulate energy, regardless of all pharmacological and dietary measures.

Ballet states that in some cases the asthenia develops in the course of convalescence but most often it makes its appearance when the general health of the patient seems to have been restored. The case of intercostal neuralgia cited above is an excellent example; the patient was supposed to have recovered from her illness when almost without warning she found herself without sufficient nervous force to make the least effort. For this type of asthenia, time and proper hygiene are the only requirements; immediate and absolute repose in bed is the primary consideration since forced effort or activity of any sort, by aggravating the asthenia, may change a temporary and unimportant complication into a state of permanent semi-invalidism. Among the numerous cases of post-influenzal asthenia, it is not unusual to observe individuals who are making an attempt to follow their normal daily routine, whether this be assuming the responsibilities of a household or engaging in business. Their friends will remark that at times they seem scarcely to have the strength to move one foot ahead of the other. In many instances, this permanent state is undoubtedly the result of a too early return to active life, with the patient forcing himself to disregard this seemingly inexplicable lack of strength. Most physicians are coming to realize the necessity for an adequate period of convalescence after acute fevers and infections, but it does not seem to be generally understood that it is because the neurosthenic function may be temporarily suppressed by the disease process.

When, as the result of forced effort during a temporary asthenia, or following trauma or emotional shock, either a permanent and incurable state or a prolonged attack of asthenia has been installed, treatment must consist mainly of the usual hygienic measures for building up the organism, with especial attention to the three fundamental principles of rest, nutrition and

elimination. In these cases, because of the relaxation of the digestive tube, there may be intestinal auto-intoxication or a tendency toward alkalosis. Foci of infection in the upper respiratory tract and teeth, thorax, abdomen or pelvis or any organic trouble should be thoroughly searched for and eradicated.

It is important to determine the gastric tolerance and arrange the diet accordingly. Usually the diet will be limited to bland, easily digested foods apportioned, if necessary, into five light meals to avoid burdening the stomach too much at one time .

Physical therapy in the form of cabinet baths, pressure sprays, light massage, ultra violet rays or diathermy will prove of value in eliminating poisons and improving the circulation, and in addition will have a good psychological effect. This form of therapy is especially valuable in cases of subjective asthenia.

Deschamps believes that where the cerebral centers are deficient, there will be an associated mineral insufficiency, especially of magnesium and phosphorus; the loss of these two minerals is the surest sign of nervous deficiency. He believes the best way to reconstitute an asthenic is to give combinations of magnesium with phosphates. Phosphorus in the form of glycerophosphates is also extensively used. Small amounts of arsenic or strychnine may be given for short periods although drugs with a tonic or stimulating effect are not well tolerated as a rule.

Wakefulness and persistent insomnia are ordinarily best combated by varying combinations of tincture of valerian, elixir triple bromides and elixir phenobarbital. The use of these drugs in equal portions and in adequate amounts is satisfactory. For extreme cases, occasional resort to codeine sulphate, gr. ¼ to ½, may be necessary once or twice in the early hours of the night to establish the somnolent state.

A certain experience with liver extract indicates that this preparation may have some substantial therapeutic value in returning the asthenic individual to his normal power although the mode of action is not known. It is our practice to recommend a tablespoonful of liquid liver extract 3 or 4 times daily for 3 to 6 weeks. Response, as indicated by an increase in the general well-being, has been noted in approximately 90 per cent of the patients so treated. While we have not yet had the opportunity of proving the efficacy of adrenal cortex hormone in the treatment of asthenia, this drug also gives promise of being valuable in certain cases. These two preparations would be expected to act by improving the general metabolism and by raising the erythrocyte count and hemoglobin and not by any direct influence on the deficient nerve center. However it is always possible that a secondary hepatic or adrenal insufficiency may have developed after an extended period in a state of objective asthenia, in which case the above remedies might have a specific effect.

Since the physicochemical state of the organism is of such significance in making a differential diagnosis and in indicating the therapeutic procedure, the required laboratory examinations should be made to detect any devia-

tions from the normal in the chemistry of the blood and urine. Where there are evidences of gastric hypoacidity, urinary hypoacidity, blood alkalosis, high blood calcium, or any other findings which suggest sympathetic predominance, vagotonic substances might be given to stimulate the parasympathetic. Various researches now being conducted indicate that posterior lobe pituitary preparations by acting on the vagus may be of value in producing gastric motility and secretion.[71]

Endocrine preparations such as desiccated thyroid substance, whole ovary substance, corpus luteum, adrenalin, pituitrin and the numerous modifications and combinations of these, have been tried with varying degrees of success. We have noted, especially in treating obese female patients with whole ovarian substance to which has been added 1/10 to 1/12 grain of thyroid extract, that a general increase in power has been obtained.

Ballet believes that the degree of asthenia probably has a relation to the degree of native insufficiency and where there are fundamental morphological and functional defects, a superimposed asthenia will be more exaggerated and more difficult to treat. Where pronounced psychic disturbances are present, the aid of the neurologist must be sought. In all cases of asthenia, however, the psychological background and the environment of the patient must be carefully studied from the standpoint of both diagnosis and treatment.

In the case of constitutional asthenia, the best advice would seem to be for the individuals to stop trying to develop themselves to normal physical and nervous capacity, but to determine what their maximum abilities are and keep slightly under that limit.

TABLE IX

PRINCIPLES OF TREATMENT

1. *Repose (the primary and fundamental treatment for asthenia)*
   - Physical, intellectual and emotional
   - Forcing the patient to activity of any sort will aggravate the asthenia and cause it to become permanent
   - After a more or less prolonged period of rest, muscular and mental activity may be gradually resumed, but this should not be permitted until the evolution toward cure is certain
2. *Explain this peculiar form of weakness and its probable future course* not only to the patient but to his family since it is usually the relatives and friends who urge the patient to exercise and move about in order to regain his strength.
3. *Make a thorough search for foci of infection or organic troubles* which may be the cause of the asthenia
4. *Institute the required laboratory procedures* for the detection of deviations from the normal in the physicochemical state of the organism
5. *Diet*
   - Give high caloric foods which are easily masticated and easily digested
   - It may be necessary to increase the number of meals in order not to burden the stomach too much at one time
   - In the acute stage, a milk, or milk and vegetable, diet may be temporarily indicated
   - Wine may be beneficial for its mild tonic action and food value, and for raising the erythrocyte count and hemoglobin
6. *Physical therapy*
   - Very light massage
   - Ultra violet light and diathermy

In the chronic cases or in the case of subjective asthenia, cabinet baths, pressure sprays, hydrotherapy, etc. are of great benefit

7. *Drugs*

Avoid drugs in general

At times, harmless doses may be given for their psychological effect

Sodium bromide is especially successful in gastric asthenia

Glycerophosphates and combinations of magnesium and phosphorus may be prescribed for the nervous deficiency

Strychnine and arsenic may be given in small doses for short periods to the calm, depressed type but will lead to aggravation in the patient with a tendency to "unnerving"

Give sedatives for insomnia

Avoid cathartics with drastic action or which cause intestinal irritation

Adrenal cortex preparations, liver extract, thyroid and ovarian substance, adrenalin, pituitrin, etc. may be helpful in overcoming the asthenia

Where there is evidence of sympathetic predominance, give parasympathetic stimulants.

Neurasthenia

In the treatment of neurasthenia, Beard states that to devote the whole attention to special and local phases such as spinal or cerebral irritation, asthenopia, oxaluria, insomnia or nervous dyspepsia can never be successful. The treatment should be constitutional with special attention to local manifestations whenever they become severe but no two cases will be alike in all details. Where the subject is under treatment for a long period of time, Beard advocates giving a sedative treatment one week, a tonic the second and the third to do nothing at all. Sometimes suspending treatment acts as a therapeutic measure in itself. In his experience, the combination of electricity, massage, counterirritants and various sedative-tonic medications seemed to obtain the best results.

In cerebrasthenia as vigorous outdoor exercise as the patient can stand should be prescribed; in myelasthenia, especially in women, absolute rest in bed in quiet, if not darkened, rooms is necessary. In digestive hygiene some need to be cautioned against overfeeding and some must be coaxed to eat more than has been their custom. A milk diet may be required in some cases and in others small frequent meals of light food. According to Deschamps, neurasthenics and also asthenics possess an "irritable" weakness and on the ingestion of irritating foods or medications an atonic and hypoacid stomach may quickly become hypertonic and hyperacid. This irritable weakness extends to the whole organism, including the psychic apparatus.

In neurasthenia the psychology of the patients is of the utmost importance. Neurasthenics as a rule take a great interest in their distresses and relate their pains and symptoms in detail. Beard found that the greater the amount of intellect and the less the emotional element, the better the prognosis would be.

While in psychasthenia and neurocirculatory asthenia the fundamental etiology is different, nevertheless the therapeutic measures recommended above will undoubtedly have some beneficial influence in returning the individuals to a normal state.

Conclusions

There appears to be a regulating neurosthenic mechanism located in the

brain which ordinarily maintains each subject in an eusthenic state. The varying degrees of sthenia, asthenia and hypersthenia may be regarded as the "neurosthenic state" of an individual in contrast to the state of physical strength dependent upon size and development, nutrition, hygiene, etc.

The neurosthenic equilibrium may be disturbed by a number of factors known as "dysthenizing agents," and an abnormal asthenia or hypersthenia may result. The most common of the dysthenizing factors are pain, emotional shocks, trauma to any part of the body with an associated total loss of consciousness, sunstroke, acute and chronic infections and intoxications such as influenza and grippe, typhoid fever, tuberculosis or malaria, streptococcic infections or food poisoning.

A differential diagnosis is of the utmost importance since muscular energy may be diminished by a number of factors and states produced which at times may be difficult to distinguish from asthenia.

Asthenia occurring as a complication of various disease states is of no especial significance and will disappear when the neurosthenic equilibrium has righted itself. Immediate and absolute repose in bed and proper hygiene are the only therapeutic requirements. Forced effort or activity of any sort, by aggravating the asthenia, may change a temporary and unimportant complication into a state of permanent and incurable semi-invalidism, as may be observed in the innumerable post-influenzal cases where the patients, because they disregarded the asthenia and forced themselves to return too soon to an active life, have never since been able to regain their normal state.

In order to carry on, these individuals must recognize their physical and mental capacity and limit their activities at a point just under their maximum ability. Small amounts of drugs with a mild stimulating or tonic action or light wine may be given; various combinations of phosphates for the nervous deficiency, biological preparations such as liver extract, adrenal cortical hormone, ovarian, thyroid and pituitary substance, and physical therapy may be of value in overcoming the asthenia.

A study of this subject suggests that, due to the high tension living of the present age, the traumas, emotional shocks, familial and financial cares and the waves of infection which seem to spread over communities, the profession must be prepared to encounter a state of asthenia more frequently than has been the case in the past.

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The Clinical Study of the Atrophic Tongue

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THE bald tongue has been recognized for many years by clinicians. Its association with anemia was probably first appreciated in 1846 by Dawson.[1] In 1909 William Hunter[2] concluded an argument for the infectious origin of the glossitic, gastric and intestinal lesions of pernicious anemia with the statement "that the most important of these signposts (glossitic) is the one which can be earliest recognized and kept in sight from the first to the last". The strength of this position was universally conceded by students of the subject; but renewed interest in and attention to the close scrutiny of the tongue in pernicious anemia arose from an appreciation of the remarkable transformation in its surface markings that attended liver therapy. Furthermore a peculiar glossitis with ultimate atrophy has been described in a wide series of clinical entities; and from this analogy a possible interrelationship is receiving increasing consideration.

This growth in the clinical importance of the subject impressed the need for an objective method of preserving the changing picture of the lingual markings. The methods pursued are recounted elsewhere.[3] After devious trials smoked paper, as suggested by Isaacs, Sturgis, and Smith,[4] afforded the best results (figure 1). With practice a quite constant technic was developed; and dipped in shellac these tongue prints constitute permanent records of inestimable service in evaluating progress.

Particular interest in the present relation attaches to the study of the lingual changes in pernicious anemia. Hunter[2] characterized the histologic picture as of an acute and subacute inflammatory nature succeeded by degenerative and atrophic changes. Round-celled infiltration in the tissues and the walls of the blood vessels of the tongue mark the inflammatory stage, whereas atrophy of the epithelium succeeds necrosis and mucoid degeneration. In the late stage a thin fibrous sheet replaces the epithelium and deeper penetration of connective tissue into the musculature indicates the extent of the preceding inflammatory process. The actual total mass of the tongue is reduced through muscular as well as epithelial atrophy.

An advanced stage in the glossitic picture is represented by

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Case I, C. F., a white farmer aged 54 years, who was readmitted in the second relapse of pernicious anemia, December 1, 1931. Combined degeneration of the cord had been established on the earlier admission 4½ years previously; but the hematopoietic response to liver had been satisfactory and many of the signs of neurologic involvement had disappeared with improved strength and muscle tone; so that on his return to the farm the patient had been able to resume his work. An injury to the left ankle eight weeks prior to readmission initiated a decline which was marked by weakness, breathlessness, paresthesias and rectal incontinence. Neglect of liver therapy was admitted. Gross evidence of cord involvement was established in absent deep tendon reflexes in the legs, loss of vibratory and position sense, ataxia in all test movements and lack of sphincter control. The tongue was completely bald and glistening. The hemoglobin registered 45 per cent and the erythrocytes 1.8 million on admission. Bronchopneumonia terminated life before liver therapy and transfusions could effect any appreciable change in the blood picture. Of particular interest in the necropsy findings was the hyperplastic bone marrow. The histologic study of the tongue (figures 2 and 3) revealed a total absence of papillae. The epithelium was thinned in areas and there was marked round-celled infiltration beneath the epithelium as well as about the smaller arterioles.

Soreness of the tongue is a common complaint among patients suffering from pernicious anemia. Yet a minority of these patients may entirely escape this subjective discomfort. Disturbances of taste are less common. Characteristic is the marginal injection of the tongue with tiny vesicles here and at the tip. These vesicles tend to rupture and leave denuded areas. The beefy redness and vesiculation are periodic and shifting in occurrence. Succeeding this stage of inflammation, denudation is the rule; but there is no relation between the severity of the inflammation and the degree of the ultimate atrophy of the papillae, nor does the former give any prognostic information as to the time of appearance of the latter. Hunter[2] recorded the occasional subsidence of the acute glossitic manifestations with the advance of the anemia, but added that in other cases such was not the case until atrophy of the papillae was complete. Not infrequently glossitis may antedate the anemia. In other individuals with advanced anemia the tongue changes may be insignificant.

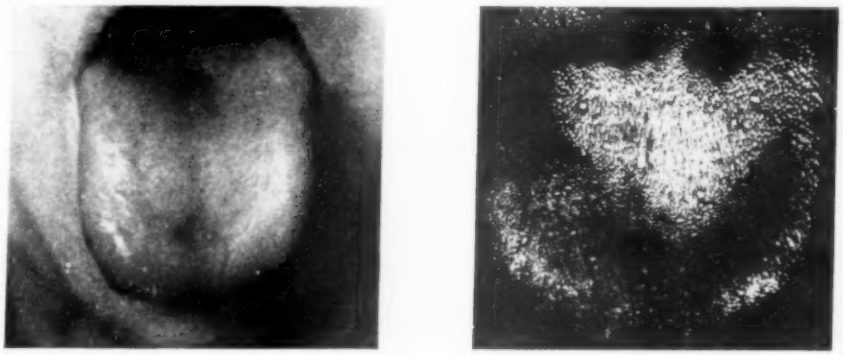

FIG. 1. Contrasting a photograph and a smoked paper print of a glossitic tongue with some degree of atrophy, taken on the same day.

As has been remarked, the introduction of liver into the therapy of pernicious anemia completely altered the sequence of events. Minot and Murphy[5] noted that "the distressing tongue symptoms so characteristic of pernicious anemia usually vanished soon after liver was taken. Vesicles on the edges and tip of the tongue disappeared as did the red-streaked, raw, or beefy appearance. The sense of rawness or pain in the esophagus subsided. In a few patients who had a pronounced disorder of the central nervous system, the disappearance of the tongue symptoms and signs was less rapid. In none of the patients who have continued the diet well have the tongue symptoms either persisted or returned. Within a few months the tongue has usually lost its shiny appearance entirely and has appeared normal."

An unusual experience is cited in Case II:

A. H., a white laborer aged 62 years, was

FIG. 2. Microscopic appearance of the glossitic tongue of Case I (low power—x 70). (Courtesy of Dr. Gorton Ritchie.)

elsewhere reported as a typical example of the recidivistic tendency of certain pernicious anemia patients under liver therapy. Beginning with his original admission, February 15, 1927, each of five successive relapses was attended by erythrocytic counts ranging from 740 thousand to 1.35 million. Not until his last two admissions of December 14, 1929, and November 20, 1930, was there the slightest evidence of neurologic involvement as manifested by a debatable obtunding of the vibratory sense in the left lower leg. On each occasion of relapse the tongue showed marked atrophy of the papillae to complete baldness. Improvement in the lingual condition anticipated the complete blood remission. In the four periods of observation where accurate notes of the return of papillae to the tongue were made, the hemoglobin and erythrocyte figures were 60 per cent with 4.07 million, 58 per cent with 3.37 million, 55 per cent with 3.83 million, and 55 per cent with 3.65 million, respectively, at the time of papillary reappearance.

The relatively close coincidence of these figures stimulated a study of this detail, but the circumstance is apparently strictly individual and dependent upon other factors than hemoglobin

FIG. 3. Microscopic appearance of the tongue of Case I (high power—x 240). Courtesy of Dr. Gorton Ritchie.)

and erythrocyte levels. In this particular instance the normal surface markings were always restored to the tongue before the blood reached a satisfactory level. Because of the patient's low mentality no accurate information was afforded of the chronologic order of glossitic symptoms and hematopoietic decline upon neglect of liver therapy. At no time during hospitalization were there evidences of acute glossitis.

The tongue prints have afforded accurate records in following the progress of the glossitic changes in pernicious anemia under liver therapy. From the evidence now available, the filiform papillae first disappear, particularly from the tip and the edges of the tongue. Thereafter the fungiform papillae are lost. The position of the circumvallate papillae renders their inclusion in tongue prints of this order impracticable; but apparently they escape gross involvement even in severe degrees of glossitic atrophy—a circumstance which may explain the preservation of the gustatory sense in many patients with pernicious anemia under such conditions. The tongue markings frequently begin their return toward normal long before the general and the hematopoietic responses to liver or its equivalent have been satisfactory, as related in Case II. The order of visible return of the papillae is the reversal of their order of disappearance. The fungiform papillae usually become distinctly prominent and then the filiform projections rapidly fill in the intervening spaces to render the fungiform papillae much less evident. The transformation of the smooth, glistening tongue of pernicious anemia to a normally surfaced member is a striking objective result of liver therapy (figure 4); but there is no apparent parallelism between the lingual and the hematopoietic responses to this form of treatment. The tongue may return to apparent normality as early as two weeks after the institution of adequate liver therapy.

Wider experience has refuted the assertion of Minot and Murphy[5] rela-

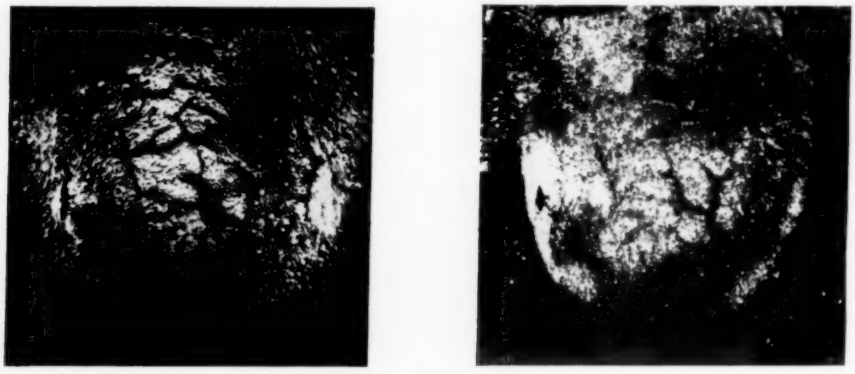

FIG. 4. Illustrating return of filiform papillae in the atrophic tongue. The filiform papillae in the second print almost obscure the fungiform elements which are so prominent in the first print.

tive to the permanency of the glossitic remission. In an overwhelming majority this advantage is maintained, provided the dosage of the effective maturating factor is held at a sufficiently high level. Most of the recurrences of glossitic manifestations in the Wisconsin General Hospital have attended efforts to establish the maintenance dosage of liver or its equivalent by gradual withdrawal, or an intercurrent infection which has reduced the efficacy of a previously adequate dosage. Isaacs[6] has made an especial study of the cyclic trend of relapses in pernicious anemia. In periods of seasonal depression glossitis of a mild order may, in his opinion, recur as a manifestation of such a relapse. As a rule, regardless of the background, the lingual changes may be controlled by increasing the amount of liver exhibited, although Isaacs, Sturgis and Smith[7] feel that "the ingestion of liver does not seem to be entirely specific for this symptom".

Second in order of frequence as a cause of the atrophic tongue in temperate climates comes simple achlorhydric anemia of which Case III is a classical example:

Case III. Mrs. A. E., a white housewife, aged 44 years, was admitted primarily for a chronic arthritic affection. The inventory by systems afforded some insight into vague digestive disturbances with intolerance for pork and onions. For nine months little meat had been eaten but the patient had partaken abundantly of fresh vegetables. Soreness of the tongue and mouth had been remarked for several months when "acid" foods were eaten. Citrus fruits would occasion serious distress, but lettuce and butter were craved. The menstrual cycles were regular. Of particular interest in the present relation were the physical observations of pallor and lingual atrophy. The tongue was raw in appearance and practically devoid of papillae. On admission the hemoglobin was 50 per cent and the erythrocytes 4.1 million. No free hydrochloric acid was demonstrable in the gastric contents even after histamine injection.

A conclusion of simple achlorhydric anemia was derived and the therapeutic trial of liver extract initiated. After two weeks of liver extract in adequate doses the hemoglobin was 45 per cent and the erythrocytes 4.2 million. Thereupon the treatment was shifted to Blaud's mass 4 grams daily and diluted hydrochloric acid 4 c.c. three times a day. The gain both from a clinical and from a laboratory standpoint was progressive from this time; so that two months later the hemoglobin registered 85 per cent and the erythrocytes 5.6 million. A month after the initiation of iron and hydrochloric acid therapy there was first noted a return of papillae to the anterior portion of the tongue. At this time the hemoglobin was 57 per cent and the erythrocytes 4.52 million. Clearly the lingual improvement anticipated any appreciable amelioration in the blood picture.

Simple achlorhydric or microcytic anemia has received wide attention in the recent medical literature at the hands of Kaznelson,[8] Watkins,[9] Witts,[10, 11] and others. Witts[10] reported glossitis in 25 per cent of 50 cases of simple achlorhydric anemia. The frequency with which frank changes to inspection were unattended by subjective complaint, led him to the conclusion of a much higher incidence. The clinical course of the glossitis to its ultimate atrophic stage can scarcely be distinguished from similar changes in pernicious anemia. In a series of cases under observation at the Wisconsin General Hospital the response to iron and diluted hydrochloric acid in full doses has followed the course of Case III. Occasional instances of simple achlorhydric anemia have been

encountered in which there has been no return of the lingual papillae in spite of a complete remission in the blood picture. The impression gathers that the lingual and the pharyngeal manifestations of this condition are much less amenable to treatment than the analogous states in pernicious anemia. Liver has not been effective in the treatment of simple achlorhydric anemia.

A somewhat less frequent situation attended by the atrophic tongue is represented in Case IV:

Case IV. Mrs. M. P., a white housewife aged 41 years, complained of choking and difficult swallowing. A "nervous" constitution had given way to emotional outbursts over a period of four or five years. Vasomotor instability was evinced in hot flashes. For 1½ years inexplicable attacks of dyspnea had occurred paroxysmally without reference to effort. A sensation of tightness in the throat with occasional inability to swallow comfortably had recurred at intervals for ten years and more recently had lead to choking. Preceding the dysphagia for about ten years the patient had experienced repeated soreness of the tongue. In her judgment both of these conditions were becoming progressively worse. Pertinent to the present consideration were the marked pallor of the skin and mucous membranes, the atrophic tongue and the palpably enlarged spleen. From time to time during the hospital stay superficial apthae appeared in the mucous membranes of the nose and throat. The hemoglobin was 48 per cent and the erythrocytes 4.2 million on admission. The icterus index was 5 and the stools showed no ova nor parasites. There was no urobilinogen in the urine. The basal metabolic rate was determined as -3 and -2. Inability to pass the stomach tube precluded a determination of the acidity of the gastric contents.

This case fulfilled the diagnostic criteria of the Plummer-Vinson syndrome. Accordingly a close inquiry was made into her dietary and no essential principle was found lacking. Milk, cream and butter were taken adequately, whereas eggs were not well tolerated. Fruits, except the citrus variety, and greens were enjoyed. Citrus fruits seemed to aggravate the soreness of the tongue and the dysphagia. Cereals, vegetables and puddings ranked as favorite foods. Meat was eaten sparingly; but the patient professed an appetite for the fat of meats as well as for butter. She volunteered the information that she had always been anemic and had taken "blood" medicine as long as she could remember.

After two weeks of Blaud's mass 4 grams daily and diluted hydrochloric acid 6 c.c. three times a day, the hemoglobin rose to 70 per cent and the erythrocytes to 5.49 million. Coincident with the improvement in the blood picture the dysphagia became decidedly better and papillae returned to the tongue.

The so-called Plummer-Vinson syndrome was first described by Vinson[12] in 1922, since which time the literature has contained scattered references to the subject. (H. S. Plummer had applied the term hysterical dysphagia to this condition in 1914). The majority of these contributions have merely added further examples of the condition or have sought to explain this obscure syndrome of glossitis, dysphagia and anemia, which usually responds miraculously to the passage of the esophageal sound. Moersch and Conner[13] reported glossitic changes in 11 of 65 cases. The tongue is commonly quite painful and sensitive.[14] Jones and Owen[15] described the smooth, glazed tongue as devoid of all papillae or with irregular islands of persisting epithelium. Witts[16] noted the close similarity of the glossitic changes in this condition to those of pernicious anemia, but expressed the opinion that aphthae and circular areas of denudation were more common in the Plummer-Vinson syndrome. Witts likewise reported the tendency for the lingual

changes to undergo a complete remission *pari passu* with the general improvement. Occasionally a residual island of atrophy may persist. While achlorhydria is the rule, the administration of diluted hydrochloric acid apparently has no beneficial effect.[16] Liver, also, is without specific action. The anemia responds most readily to transfusions, and iron is commonly effective as in Case IV.

The streptococcus was adjudged the responsible etiologic agent in the glossitis of pernicious anemia by Hunter.[2] Schneider and Carey[17] isolated the streptococcus viridans in cultures from the deeper layers of the tongue and demonstrated this organism deep in the muscles of the tongues of pernicious anemia patients studied by biopsy. The scope of the present discussion does not admit of a consideration of the probable significance of this finding; but the overwhelming weight of evidence favors the contention that the streptococcal invasion of the tongue is incidental rather than causal in pernicious anemia. A rather striking example of streptococcal glossitis is cited in Case V, because of the etiologic problem it suggests.

Case V. Miss J. J., a white nurse aged 40 years, complained of a sore mouth. For three years the gums and tongue have been almost continuously sore. Since the age of 16 years the patient has been periodically troubled with canker-sores on the gums, buccal mucous membranes and tongue. Lately the lips have become dry and sore. Occasionally a vaginal discomfort, likened to that of a canker sore, has been remarked by the patient. Unexplained subcutaneous hemorrhages have occurred in two fingers in the past nine months. For seven or eight years recurrent swelling of the right upper eyelid has developed at irregular intervals. Fatty foods were not well tolerated. Citrus fruits and tomatoes were avoided because of the discomfort which they induced locally in the mouth. The mouth was the chief seat of pathologic findings to physical examination. The mucous membrane of the entire mouth and oropharynx was deeply injected and sensitive. The tongue was beefy with especial congestion at the tip and edges. Transverse furrows were apparent over its dorsum and the papillae were quite atrophic. Sublingual soreness and bogginess were observed. The gustatory sense for sour and bitter was lost, but sweet was promptly perceived. The hemoglobin was 75 per cent and erythrocytes 4.6 million. Free hydrochloric acid appeared in the gastric contents only after histamine. Repeated cultures of the tongue scrapings showed streptococci in overwhelming predominance. Sensitization tests for food, keratinoids and streptococci proved negative.

Nor do these examples exhaust the clinical conditions which are attended by the atrophic tongue. Probably the tongue of sprue most closely approximates that of pernicious anemia. Manson-Bahr and Willoughby[18] gave a comprehensive consideration to this detail. The earliest manifestation in their experience was an increased sensitiveness to hot fluids, spices and tobacco smoke followed by a perversion to salt and to sweets. The fungiform papillae were seen to stand out prominently toward the tip of the tongue as hyperemic dots. Aphthous ulceration of the buccal mucous membrane and tongue occurred on the rupture of tiny vesicles in their deeper layers. These aphthae induced marked tenderness and sensitiveness in the parts affected, especially the inner margin of the lower lip, the frenum, tip and sides of the tongue and less commonly the mucosa of the cheek opposite the lower molars. The chronic sprue tongue was smooth and polished. In their judgment, while the oral symptoms may recur or persist

after the gastro-intestinal situation has been controlled, "it is a useful guide to consider a patient with obvious tenderness of the mucosa of the mouth and with unrestored function of the filiform and fungiform papillae as incompletely restored to health. . . . The tongue and mouth should constitute an index of what is going on in the rest of the alimentary tract."

In pellagra, ulceration of the tongue is not uncommon along its edges. This ulceration may eventually lead to a complete denudation and the tongue assume a beefy redness. At this period mastication may be extremely painful and deglutition a torture. Again, widespread ulceration may be unattended by serious distress. The latter circumstance doubtless arises from the mental deterioration of the pellagrin in many instances. The deeper injection and the firm, sharp contour of the pellagrous tongue are in contrast to the moderately congested and flabby tongue of sprue. Denudation rather than atrophy accounts for the smooth tongue in pellagra. The response of the glossitic manifestations to proper dietetic management is one of the earliest measures of its success.

The anemias of pregnancy and the puerperium are frequently attended by soreness and atrophy of the tongue.[19] As a matter of fact the early descriptions of pernicious anemia attended by atrophy of the tongue were in several instances[20, 21] classical examples of the anemia of pregnancy. Keefer and Yang[22] observed glossitis with atrophy in malnutrition attended by dysentery and anemia. Relief of the underlying condition resulted in a return of normal papillae. Lewis[23] noted glossitis with low papillae in a case of pyloroplasty complicated by peritonitis and obstruction for which a jejunostomy had been performed. Meulengracht[24] reported atrophy of the lingual papillae with injection and blebs succeeding intestinal stricture, in a review of the blood changes attendant upon this condition. Isaacs, Sturgis and Smith[4] noted the tongue in dibothriocephalus latus infestation to be smoother than normal but not atrophic. Glossitis with atrophy of the tongue has been observed in achlorhydria by Schneider and Carey[25] among others. Wilkinson and Oliver,[26] for example, found a sore tongue or an ulcerative stomatitis the outstanding feature in 25 of 53 cases with achlorhydria. Oatway and Middleton[3] found a definite correlation between gastric anacidity and lingual atrophy. Witts[11] admitted the common coincidence of achlorhydria and glossitis, but pointed out the occurrence of the latter in certain cases of anemia and malnutrition in which the free hydrochloric acid of the gastric contents was normal.

From this review it may be concluded that glossitis with ultimate atrophy occurs in a considerable group of conditions. It is beside the purpose of this presentation to hypothesize as to the possible significance of this circumstance. Lewis[23] in a comprehensive survey of the subject, concluded that "there is no general agreement as to the cause of lingual atrophy in any of the conditions considered", although he clearly leaned toward a conditioned deficiency as the background. Castle and his fellow-workers[27] advanced further evidence in support of this position. Whatever the final answer to this question may be, the clinical significance of these lingual changes.

both in the diagnosis and the prognosis of the conditions discussed, must not be overlooked. To this end the advantage of serial tongue prints as a means of studying the progress of the glossitic process is strongly urged.

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The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection

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FEVER, one of the most constant and striking features characteristic of the invasion and growth of pathogenic microörganisms, has attracted the attention of physicians since the beginning of medicine. Hippocrates, Celsus, Sydenham and many others considered it of importance as a defensive mechanism against disease, *"vis medicatrix naturae"*. This viewpoint prevailed generally until the nineteenth century when a number of observers took an opposite stand. Claude Bernard, Liebermeister and others devoted much attention to fever and believed it to be harmful. Their opinion in regard to the deleterious effect of fever on the body appeared to be greatly enhanced by the contemporary development of cellular pathology and the demonstration of "cloudy swelling" as a result of fever by Virchow. Their publications were widely accepted and led to the adoption of various measures for the purpose of reducing fever. Naunyn was one of the first to attack Liebermeister's teaching, and showed that fever in itself was not responsible for the various pathological changes often found in febrile diseases, but that the damage was caused primarily by the invading organisms. It was admitted that extremely high or prolonged fever, as for instance in heat stroke, often produces pathological changes in tissues.

Recent clinical and experimental studies also show that excessively high body temperatures, induced artificially are harmful and may prove fatal.

Controversy in regard to the harmful or beneficial effects of fever reached its height late in the nineteenth century. The weight of evidence now appears to favor the latter contention. Experiments designed to show the beneficial influence of fever as a defense mechanism against bacterial infection may be divided into four classes,—the demonstration of (a) antibacterial and antitoxic effects of fever temperature *in vitro*, (b) the enhancement of antibacterial and antitoxic ability of the host by raising the body temperature, (c) the diminished resistance of the host to bacterial infection by lowering the body temperature, and (d) the beneficial effects of intercurrent infection and fever on other diseases.

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As early as 1876 Heydenreich[1] noted that the spirilla of relapsing fever lost motility sooner at 40° C. than at normal body temperature. Many other studies later showed that bacterial growth appears to be inhibited by temperatures over 40° C.[2, 3] Yoshioka[4] showed that pneumococci, when grown at 39° C., lost both virulence and specificity. Vibriolysin and tetanolysin were destroyed by heat *in vitro*, and guinea pigs heated by light treatment were more resistant to these toxins than unheated animals, according to experiments of Sonne.[5]

Filehne, Chienisse, Walter[1] and Trudeau showed that animals kept warm or heated were less susceptible to experimental infection than those whose temperature was lowered. Recently, Robertson,[6] in observations on experimental pneumonia in dogs, noted that when morphine was given in quantities sufficient to produce a well marked depression of body temperature, subsequent infection with pneumococcus resulted in a severe, prolonged and widespread infection often accompanied by bacteremia and ending in death. The same quantities of pneumococci in unmorphinized dogs produced a mild localized disease lasting two or three days. Rolly and Meltzer,[7] in 1908, showed that heated animals were more resistant to bacterial infection that unheated ones, but were unable to demonstrate any special bactericidal substance in the blood, nor was there a constant degree of phagocytosis demonstrable in the heated animals. In other experiments, they showed that phagocytosis became more active as the temperature exceeded 37° C. until 40° was reached. Temperature higher than 40° C. interfered with phagocytosis.

Rolly and Meltzer,[7] Lüdke,[2] Friedberger and Bettac[8] and others demonstrated an increase of agglutinins and hemolytic amboceptor by heating animals. The increase in titer of typhoid bacillus agglutinins as a result of fever due to other causes has been repeatedly observed both clinically and experimentally. The fact that chronic diseases are occasionally favorably influenced by intercurrent acute infection has been known for many years and has led to the common usage of hot baths and heliotherapy, which were already used by the ancients. In modern times, the inoculation of malaria or relapsing fever parasites, the injection of foreign protein or the use of diathermy are widely employed for the purpose of inducing therapeutic fever.

A new approach to studies on the effects of infection and fever has been furnished by observations in regard to the suspension stability of the blood. This phenomenon although widely observed for many years, then disregarded, was restudied and popularized by Fåhraeus[9] in 1921. Since then, hundreds of papers have appeared concerning studies of the suspension stability of the blood, expressed as sedimentation time or speed of erythrocytes, in many diverse conditions.

Fever and a disturbance of the suspension stability of the blood may occur independently but usually occur together and accompany most if not all infectious diseases. The decrease of suspension stability was shown to be due to an increase of the globulin and fibrinogen content of the blood,

which occurs in most febrile infectious diseases and in certain afebrile conditions as in pregnancy and myeloma.[38] Whether fever alone is responsible for the increase of blood protein or whether it is due to effects of the invading organism has not been decided. Fåhraeus believed it to be due chiefly to the effects of the virus. Experiments by Frisch and Starlinger,[11] Puxeddo[12] and others, and studies in our own laboratory also indicate that fever alone, as induced by diathermy is not effective in causing marked increases in either globulin or fibrinogen.[39] It is probable that a combination of factors in febrile infectious disease operates to produce plasma protein changes by stimulating globulin or fibrinogen producing organs, presumably the bone marrow or the endothelial system.

With increase in the globulins, there occurs an increase in the viscosity of the plasma. Then, as a result of an alteration of electrical charges[10] the erythrocytes clump and settle rapidly. In attempting to show the beneficial effects of a decrease in the suspension stability of the blood in regard to defense against infection, Fåhraeus[10] has shown that a slowing of the blood stream such as occurs in inflammatory tissue, permits the erythrocytes to form large clumps and as such they tend to occupy the axial current of the slowly moving stream according to physical principles. As a result, leucocytes are crowded out and forced along the walls of the vessels to a favorable position for migration through the vessel wall into the area of inflammation. (See Zinsser,[13] p. 300.)

In returning to the subject of the aggregation of erythrocytes in plasma of increased viscosity, the question arises as to whether other suspended particles may not be similary affected. Leucocytes may be clumped[14] but little attention has been given to the effects of plasma changes on bacteria.[15,16] Both erythrocytes and bacteria are known to carry negative electrical charges[17] so that if erythrocytes tend to clump when the electrical equilibrium is disturbed by a change of plasma proteins, bacteria theoretically should be similarly affected. If it can be shown that the changes in the plasma which accompany febrile infectious diseases favor the clumping of bacteria, another point will be added in favor of fever and plasma protein changes as mechanisms of defense against infection. Bull,[18] Rich,[19] Cannon [20, 21] and others have shown that the agglutination of bacteria is one of the most important steps in the recovery from experimental infection.

Experimental

The following experiments were performed to determine the effect of changes of viscosity of the plasma and of other fluids on the clumping of bacteria.

Several preliminary experiments were made to test the behavior of various kinds of bacteria when suspended in samples of plasma of varying viscosity. Type II pneumococci, typhoid bacilli and Friedländer bacilli were suspended in plasma obtained from a normal individual and in plasma obtained from a patient suffering from lobar pneumonia due to type I

pneumococcus. The viscosity of the normal plasma diluted 1 in 10 with 10 per cent solution of sodium citrate was 1.7 (Hess viscosimeter) and the suspension stability was such that the sedimentation time of erythrocytes, measured from the time the level of the red cell column dropped to the 60 mark on a tuberculin syringe, was over two hours. The viscosity of the patient's plasma was 2.4 and the sedimentation time 10 minutes. There was little or no perceptible effect on the bacteria when suspended in the plasma of higher viscosity than normal. In some instances, there was a slight tendency to clump in the more viscid plasma.

Very different results were obtained when minute amounts of specific immune serum were added to the plasma. Tests were made by using immune serum obtained from a patient vaccinated with typhoid-paratyphoid A and B vaccine and paratyphoid B bacilli. Instead of preparing dilutions of specific immune serum in normal physiologic salt solution as customary, dilutions were made in parallel in normal plasma and in plasma of increased viscosity. When bacilli were suspended in the dilutions as arranged, clumping occurred in a far higher titer (1–10240) in the high viscosity plasma, than in normal plasma (1–320).

Similar results were obtained when the viscosity of normal plasma was increased by the addition of gum acacia, as shown in table 1.

The agglutination reaction shown in table 1 indicates that increase in viscosity enhances the specific agglutinative effect of specific immune serum.[22] Results similar to these were obtained in experiments with type I pneumococci and type I antipneumococcus serum, and with type b Friedländer bacilli which agglutinate specifically in type II antipneumococcus serum.

When smears stained with Wright stain were made from each tube and examined, microscopic clumping was found to occur within 10 minutes at 37° C. Bacteria suspended in plasma of high viscosity or in plasma to which acacia had been added stained with difficulty. They appeared pale and swollen or as if thickly coated with a gummy substance which prevented penetration of the dye. Capsules of pneumococci and Friedländer bacilli were often accentuated. In many preparations it appeared as if most of the organisms had vanished. Resuspension or washing the organisms in physiological salt solution restored the normal staining reaction. In most microscopic preparations made from suspensions of bacteria in colloidal solutions, bacteria appeared to be en-

TABLE 1

DILUTIONS OF SPECIFIC IMMUNE SERUM	40	80	160	320	640	1280	2560	5120	10240	20480	Control
Plasma + 2½% acacia	+++	+++	+++	+++	+++	++	+	+	+	+	±
Normal plasma	++	+	+	+	—	—	—	—	—	—	—

Microscopic agglutination of Bacillus paratyphosus B in specific immune serum diluted with high viscosity plasma (upper row) and with normal plasma (lower row). Reading made after 2 hours incubation at 37° C.

meshed, even if not specifically clumped, in amorphous patches of lightly stained material presumably of the colloid itself. Bacteria suspended in plain broth or in salt solution were always diffusely scattered. Typhoid bacilli immediately became non-motile when suspended in 5 per cent solutions of gum acacia.

Increase in viscosity, as such, is apparently not alone responsible for the reactions described. Further experiments showed that solutions of other viscous substances—gum tragacanth, agar, egg white, starch paste, gelatin and glycerin adjusted to similar viscosity were less effective than gum acacia in enhancing specific agglutination.

Experiments with blood from a case of hyperinosis. Plasma obtained from a patient with myelomata contained 5.48 gm. of fibrinogen and 2.27 gm. euglobulin per 100 c.c.[23] The plasma viscosity was 7 as compared with 1.8, the viscosity of normal plasma, according to the technic used. The sedimentation time was 5 minutes. Two dilutions, one of 1-100 and one of 1-200, of type I antipneumococcus serum were prepared with the whole blood of high viscosity and with normal blood as a control. Specific antipneumococcus serum seldom causes clumping in dilution as high as 1 to 200 when tested by the usual methods. Type I pneumococci were added to each tube. Stained preparations were made after 10 minutes incubation at 37° C.

Large clumps of pneumococci were found in preparations from the high viscosity blood in both dilutions of antipneumococcus serum. The leucocytes and platelets were not involved in the agglutination process and appeared to take no part in the reaction which is in harmony with the observations of Wright[3] and others. Pneumococci were diffusely scattered in the smears made from both tubes containing normal blood and immune serum. An illustration of the type of clumping referred to is shown in figure 1.

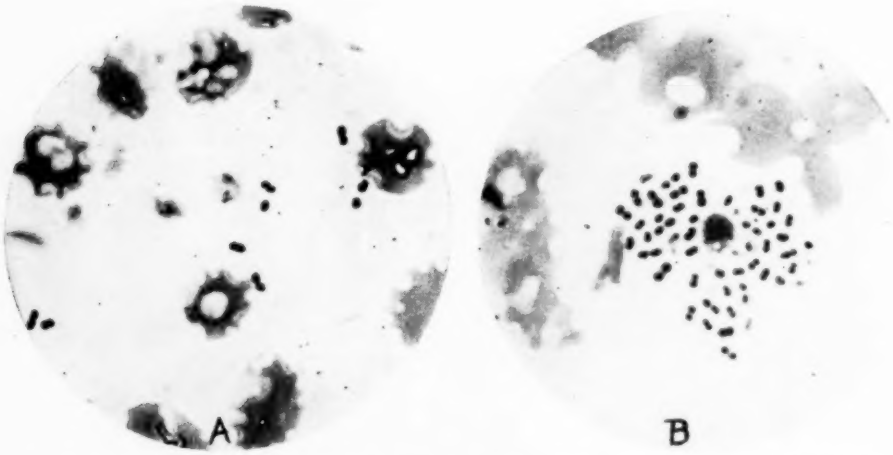

FIG. 1. Type I pneumococci and type 1 antipneumococcus serum 1-200, incubated 10 minutes with (A) normal blood, (B) high viscosity blood. Pneumococci are clumped in high viscosity blood with a minute amount of specific immune serum.

Similar results were obtained when the plasma of this patient and normal plasma were used with type II antipneumococcus serum and type b Friedländer bacilli. Clumping of bacilli occurred in dilutions of immune serum as high as 1-160 in the high viscosity plasma but only in the strongest concentration (1-10) in the normal plasma. An illustration of the clumping reaction is shown in figure 2.

were incubated for two hours. At this time stained preparations were made from the contents of each tube. The tubes were then kept in the icebox over night and read for macroscopic agglutination. The results of macroscopic agglutination are shown in table 2.

It is evident from the table that within a certain range, viscosity due to gum acacia has a striking effect on the

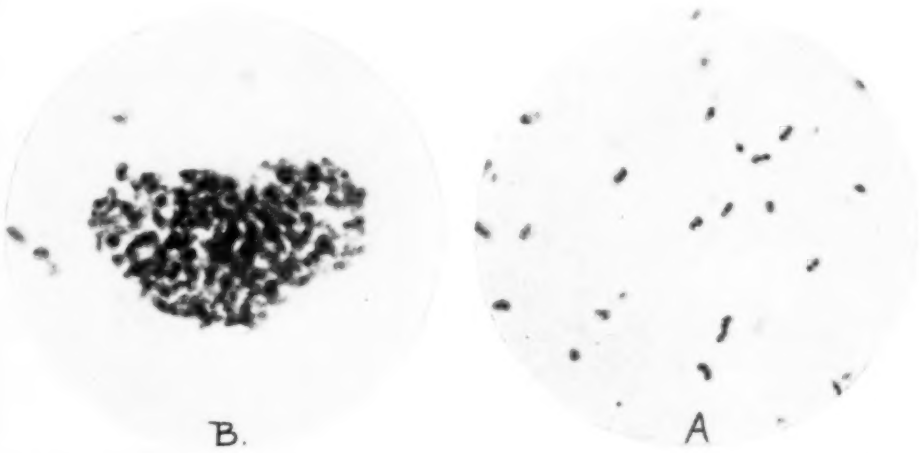

FIG. 2. Type b Friedländer bacilli and type II antipneumococcus serum 1-40, incubated with, (A) normal plasma, (B) plasma of high viscosity. Bacilli are clumped in high viscosity plasma with a minute amount of specific immune serum.

Effect of varying grades of viscosity. Tests were made to determine the effect of varying degrees of viscosity with varying concentrations of specific immune serum. The experiment was arranged as shown in table 2. A solution of gum acacia was diluted in physiological saline solution so that varying degrees of viscosity were obtained. To the series of tubes containing these dilutions, type I antipneumococcus serum was added in the dilutions indicated. Heat-killed type I pneumococci were added and the tubes

sensitivity of specific agglutinins. Increase of viscosity beyond 5.6 tends to inhibit clumping. It is of interest to note that the range of viscosity at which clumping occurs best is close to the range of the viscosity of blood during certain infectious diseases.[24] The macroscopic results described checked with the microscopic examination of the clumping reaction made after two hours incubation. Identical results were obtained when type II antipneumococcus serum and type b Friedländer bacilli were used.

TABLE 2

DILUTIONS OF TYPE I ANTI-PNEUMOCOCCUS SERUM		1-10	1-20	1-40	1-80	1-160	1-320	1-640	1-1280	1-2560	1-5120	Control
Salt solution		++++	++++	++++	++	−	−	−	−	−	−	−
Viscosity of solutions of gum acacia	1.6	++	++++	+++	++	+	−	−	−	−	−	−
	2.2	++	++++	+++	+++	++	+	−	−	−	−	−
	3.5	++	+++	+++	+++	++	++	++	++	+	−	−
	5.6	++	++	++	++	+	+	+	+	+	−	−
	8.	+	+	+	+	+	+	+	−	−	−	−
	11.	+	+	−	−	−	−	−	−	−	−	−

++++ disc formation
+++ disc easily broken up
++ coarse clumping
+ fine clumping
− no clumping

The effect of varying degrees of viscosity on the clumping of type I pneumococci in varying concentrations of specific immune serum. Viscosity from 3.5 to 8 appears to exert the maximum effect.

Effect of changes of viscosity in vivo. Mice were inoculated intraperitoneally with 0.5 c.c. of an 18 hour broth culture of type I pneumococci and divided into three groups. One group was injected intraperitoneally with .01 c.c. of type I antipneumococcus serum diluted in 0.5 c.c. of normal physiological saline solution, the second group with 0.5 c.c. of a 10 per cent solution of gum acacia and the third group with .01 c.c. of serum diluted in 0.5 c.c. of 10 per cent acacia. The injections were arranged so that all mice received similar quantities of fluid intraperitoneally. Mice from each group were killed after 15, 30 and 60 minutes. Stained films were made from the peritoneal fluid of each mouse.

Results. In mice receiving the minute amount of immune serum, pneumococci were found in great numbers diffusely scattered. The leucocytes were free and scattered. In mice injected with acacia alone, pneumococci stained poorly and many were scarcely visible, but no clumping was observed. Clumping of leucocytes was the most prominent feature. The most striking results were found in mice receiving both serum and acacia. Even at the end of 15 minutes most of the pneumococci had become invisible or had disappeared. A few tight clumps appeared here and there, either free, or attached to, or included in, agglomerations of leucocytes. Phagocytosis was slight. Leucocytes free in the peritoneal cavity appeared to take part in the clumping reaction, in contrast to their behavior in the blood. An illustration of the results obtained is shown in figure 3.

Discussion. The non-specific effect of blood colloids on specific agglutination was observed by Bordet and Streng in 1909.[25, 26] The agglutinative effect of the colloid was called conglutination and was recognized as distinct from the effects of specific agglutination. By adding ox serum Streng obtained a marked clumping of bacteria in dilutions of specific antisera which were too weak to cause agglutination unaided. He and Barikine[27] showed that conglutinin was removed by precipitating the globulin fraction of the serum. Dean[28] in 1911 reported similar observations and again showed that agglutinating serum contains two factors both of which are necessary to cause clumping; the one is a specific antibody, the other a non-specific substance which is possibly globulin. He also showed that a deficiency of the non-specific substance could be made up by the addition of globulin.

The experiments reported in this paper also show that at least two factors play a rôle in clumping of suspended organisms and that specific agglutination is influenced by various colloidal substances.

The mechanism involved in the agglutination or clumping of bacteria has received much attention. Gruber[29] in 1896 was the first to show that increased viscidity of bacteria caused them to adhere to one another and favored their subsequent englobement by phagocytes. The physicochemical principles involved in the clumping reaction have been studied by many observers. (See Northrop[30] and Zinsser[13] for references and discussion.) The outcome of much experimental

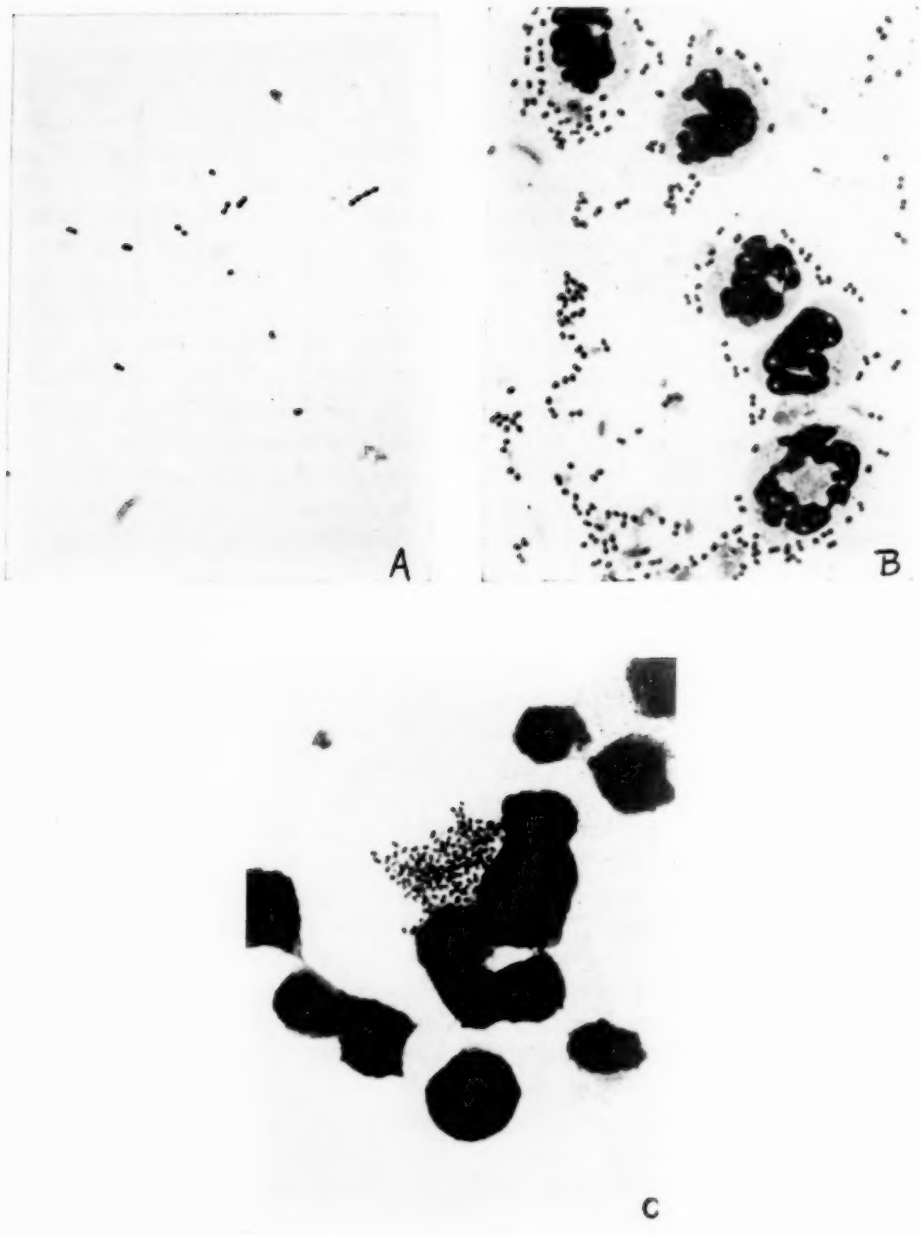

FIG. 3. Effect of viscosity on agglutination of type I pneumococci *in vivo*. (A) smear from mouse injected intraperitoneally with type I antipneumococcus serum, (B) from a mouse injected with 10 per cent gum acacia solution, (C) from a mouse injected with both serum and acacia. In A and B the organisms are diffusely scattered. In B the leucocytes tend to clump and in C both pneumococci and leucocytes clump.

work indicates the complexity of the phenomenon. Bacteria in suspension appear to behave much like other protein particles. Their agglutination and precipitation depends largely upon repulsive and cohesive forces. Changes in the composition of the menstruum in which bacteria are suspended alter the cell surfaces, bring about changes in electrical charge and cause clumping.

The experiments reported in this paper concern the enhancement of specific agglutination brought about by changes in the plasma proteins as a result of febrile infections. The reaction was shown to be influenced by increase in the globulin-fibrinogen content of the blood which increased the viscidity of the plasma. The effects of increase of viscosity of the plasma could be reproduced by increasing the viscosity by adding other colloids, especially gum acacia, to the suspension. The effects were observed both *in vitro* and *in vivo*.

Increase of fibrinogen or globulin in the blood occurs in almost all infections, but whether fever in itself is directly responsible for plasma protein changes or whether these changes merely accompany fever and both are caused by substances liberated by the virus is as yet uncertain. It appears that plasma protein changes result from the stimulation or irritation of globulin- or fibrinogen-forming organs and commonly occur in afebrile conditions (pregnancy, myeloma) as well. Studies by Lloyd and Paul[31] indicate that fever alone does not produce plasma protein changes but that the effect is dependent upon the intensity of the infection. It has been shown also that elevation of the body temperature by diathermy produced but slight and transient blood protein changes.[11] On the other hand, marked changes are caused promptly within two or three hours by the parenteral injection of protein and non-protein substances.[32] The indications are, therefore, that both fever and plasma protein changes may occur independently and are due to the effects of the virus. Studies of these factors are under way in our laboratory at present.

At any rate, I have attempted to show that the changes in the blood proteins and increase of blood viscosity which occur during infectious diseases may represent an important mechanism in the defense of the body against infection. A number of observers[18, 19, 20] have shown that agglutination is an important factor in the defense mechanism of the host. Mudd[33, 34] and his associates have shown that increase of cohesiveness closely parallels increase in phagocytosis. It has been shown in this study that the optimal degree of viscosity produced artificially *in vitro* closely approximates the degree of viscosity of plasma found to exist during infectious disease and that this viscidity favors agglutination of bacteria. Whether these changes are of teleological significance is difficult to say. The effects discussed are non-specific and mechanical in nature. The fact that increases of blood colloids appear to prepare bacteria for clumping and ultimate phagocytosis permits one to regard the phenomenon in the nature of an opsonin.

Certain instances at first appear to contradict the suggestion that increase of viscosity due to increase of blood globulin is an important factor in de-

fense against infection. It is known that diseases like kala-azar and leukemia, are peculiar in that they are accompanied by marked increase of the plasma proteins, yet they particularly predispose the patient to secondary infection. It has been shown,[35] however, that in the diseases mentioned there appears to be an inability to elaborate specific antibodies. The data presented in this paper indicate that increases in viscosity in the absence of specific immune bodies are without effect. A further and more contradictory example pertains to the fatal infection from avirulent R pneumococci in horses used for the production of antipneumococcus serum.[36] In this instance, horses whose blood is known to be exceptionally high in fibrinogen content had been highly immunized by the intravenous injection of living S pneumococci, yet in the presence of high specific immunity and high fibrinogen content of the plasma, they succumbed to infection.

Other evidence of the effect of increase of viscosity on specific agglutination has developed from an entirely different approach. Fitch, Donham, Bishop and Boyd[37] have shown that the presence of agar greatly enhances the specific agglutination of organisms of the Brucella group. They have applied the phenomenon to practical purposes in agglutination tests.

The demonstration of the increase of the effective range of agglutination by specific immune serum by increasing the viscosity of the menstruum raises a number of questions for future investigation. One pertains to the apparent non-specific reactivation of agglutinins during infectious diseases, as for example, the reappearance of typhoid agglutinins during other infections. During and after lobar pneumonia, to what extent does the increase of the agglutination titer of the patient's blood depend upon the strength of the specific immune bodies or merely upon the increase of the globulin or fibrinogen? A relationship between the suspension stability of the blood and the titer of specific typhoid agglutinins has already been noted by Vorschütz[15b] and others. Finally what are the potentialities of increasing therapeutic effectiveness of specific immune serum by increasing the viscosity of the plasma by dietary or other measures?

Summary

Evidence has been presented by many observers to show that fever exerts a beneficial influence in the defense mechanism against infection. It has been shown that temperature at fever levels tends to influence the growth of bacteria adversely, to diminish the potency of toxins, to favor phagocytosis and to stimulate the development of immune bodies.

In experiments reported in this paper it has been shown that the increased viscosity of the plasma which occurs during febrile infection as a result of increase of certain plasma proteins enhances the specific agglutinative power of specific immune serum. Other investigators have shown that agglutination is an important factor in the restriction of bacterial growth and spread in the tissues. It is therefore suggested that the plasma protein changes which occur during infectious disease and enhance agglutination are important factors in the defense mechanism against infection.

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Poisonous Spider Bites

Newer Developments in Our Knowledge of Arachnidism

By

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INCIDENCE OF ARACHNIDISM

ALTHOUGH poisoning resulting from the bite of a spider has been recognized from the earliest times, and instances were noted in this country more than two hundred years ago,[136] a review of the literature made in 1926 disclosed a remarkable amount of skepticism as to the real existence and seriousness of this condition. At that time more than one hundred and fifty cases of spider bite poisoning reported by more than thirty different observers in the United States were reviewed, fifteen cases studied at the Los Angeles General Hospital were presented, the clinical syndrome was described at length, the course and treatment outlined, and some experimental work on the effect of the venom on small animals was summarized.[22]

In the five years that have elapsed since this work was published, arachnidism has become much better known in this country and cases are being recognized and reported with considerable frequency. Thus more than a dozen different authors have published accounts of over seventy-five additional cases of arachnidism in this country, and numerous reports have appeared in Australia, South America and elsewhere, on this subject. Personal communications have revealed more than a hundred other cases, hitherto unpublished, treated by a score of physicians in California, Florida, and other states.

In view of the fact that nineteen instances of this condition were seen at a single hospital in Los Angeles during the past year, it appears probable that the true incidence of the disease throughout the country annually exceeds hundreds, and possibly thousands, of cases. Several death certificates were made out from this cause in California during the past year and several others reported in the newspapers and in personal communications, so that even though the mortality rate is very low, the possibility of such fatal termination cannot be disregarded.[11,37,129,148]

By far the greatest number of poisonous spider bites in human beings have been attributed to the black widow, or shoebutton spider, the female *Latrodectus mactans;* and to related species in other countries. It is true that a few instances of poisoning due

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TABLE I

Poisonous Spider Bites in the United States

STATE	CASES	DEATHS	STATE	CASES	DEATHS
Alabama	17	0	Nebraska	0	0
Arizona	x	0	Nevada	x	0
Arkansas	6	0	New Hampshire	x	0
California	250	12	New Jersey	0	0
Colorado	1	0	New Mexiço	x	0
Connecticut	0	0	New York	x	0
Delaware	0	0	North Carolina	9	1
Florida	35	0	North Dakota	0	0
Georgia	7	0	Ohio	1	1
Idaho	0	0	Oklahoma	2	1
Illinois	0	0	Oregon	0	0
Indiana	0	0	Pennsylvania	2	0
Iowa	0	0	Rhode Island	0	0
Kansas	2	1	South Carolina	x	0
Kentucky	x	0	South Dakota	0	0
Louisiana	12	0	Tennessee	1	0
Maine	0	0	Texas	5	0
Maryland	1	0	Utah	x	0
Massachusetts	1	0	Vermont	0	0
Michigan	0	0	Virginia	27	1
Minnesota	0	0	Washington	0	0
Mississippi	x	0	West Virginia	1	0
Missouri	0	0	Wisconsin	0	0
Montana	0	0	Wyoming	0	0

Total: 380 cases with 17 deaths in 18 states.

(x=Black Widow Spider identified but no bites reported)

to the bites of other kinds of spiders have been reported,[143] but in most instances these bites have resulted in local rather than in general symptoms, [160] and many cases have been so complicated by infection and other factors that a correct evaluation is impossible.[37] On the other hand, the female *Latrodectus mactans* has been observed in scores of instances, and its recognition established not only by the very vivid descriptions of the black spider and its red markings given by the patients, but on many occasions the actual specimen has been captured and submitted to competent authorities for identification.

Moreover, the astounding symptoms which develop after the bite of this spider are so striking and unique that there seems to be little danger of confusing it with any other form. Further experimental work with the spider and extracts of the poison glands in our laboratory have, for the most part, confirmed previous findings. The bite of the spider produced marked symptoms, sometimes fatal, in mice as well as in rats, in many but not all of the experiments so performed. As previously reported, however, no consistent effect was obtained by the injection of macerated extracts of the whole spider or of its glands alone into mice,

rats, guinea pigs, rabbits, cats or chickens.[22, 26]

The question arises whether there has been an actual increase in the number of cases of spider bite poisoning in this country, or whether the condition is simply being more often recognized. The numerous occasions

TABLE II
Incidence of Poisonous Spider Bites

YEARS	NO. CASES REPORTED
1720	1
1800-1825	0
1825-1850	5
1850-1875	7
1875-1900	116
1900-1925	85
1925-1932	166

on which physicians, being told of the syndrome, recall similar cases which they had seen in the past and failed to diagnose correctly, suggest that the latter explanation is by no means unreasonable. On the other hand, numerous observers have noted an actual increase in the number of the spiders, and particularly a change in their habitat, so that now, instead of being confined mainly to little inhabited rural regions, they appear to have invaded the city homes and are frequently found within garages and bedrooms of populated houses.

Accounts are still being received of patients suffering from the bite of the black widow spider who were subjected to the additional trauma of a major surgical operation because of faulty diagnosis and confusion with acute surgical conditions.[38, 69, 85, 129, 147] It is, therefore, again in order to call attention to the existence and semeiology of this very interesting but not really rare condition.

Altogether sixty patients suffering from the bite of a poisonous spider have been treated at the Los Angeles General Hospital. The findings

TABLE III
Cases of Arachnidism at the Los Angeles General Hospital

YEAR	NO. CASES
1915	1
1916	0
1917	0
1918	0
1919	1
1920	1
1921	0
1922	1
1923	2
1924	2
1925	8
1926	7
1927	2
1928	2
1929	2
1930	12
1931	19
Total	60

of the earlier studies have been quite consistently confirmed, and additional information has been obtained in this larger group. Most of the patients were men, but seven, or twelve per cent, were females. The ages ranged from one to seventy-two years, but the majority were young adults. The

TABLE IV
Age and Sex

YEARS	MALE	FEMALE	TOTAL
0- 9	4	1	5
10-19	9	0	9
20-29	18	2	20
30-39	9	0	9
40-49	5	0	5
50-59	4	2	6
60-69	3	2	5
70-	1	0	1
Total	53	7	60

majority were native white Americans but seventeen Mexicans and five Orientals were included. Nearly half of the patients were common laborers, but six housewives, nine children, and more than a score of skilled workers, including a sheriff, a painter and a teacher were affected.

Most of the bites occurred in the more sparsely settled districts, the majority of them being entirely outside of the city limits of Los Angeles, but instances were noted in the more crowded neighborhoods also. The bites took place, for the most part, in the evening or early morning in summer or autumn. The spider was seen and described in the majority of instances, but a number of cases were diagnosed from the characteristic clinical picture alone, often confirmed thereafter by a successful search of the premises for the spider.

The culprit was variously described as large, medium sized or small, but always as black, and smooth or shiny, and usually as being marked with red on the abdomen, especially on the ventral side, where the hourglass shape of the red mark was often noted. Many of the spiders, alive or dead, were brought in for recognition. They were located in an outdoor privy in half of the cases, but in this series there were ten patients who were bitten while in their own homes, most of them while in bed. Several cases occurred in automobiles or garages, and in several the spider was found in clothes which had been hanging in exposed places, on porches, garages, in yards, etc.

The site of the bite was on the penis or neighboring structures in half of the cases, but the extremities were bitten in sixteen instances, the body ten times and the head twice. This is a much higher incidence of extragenital localizations than has been previously reported, due to the fact that the spiders in the more recent cases has been found more often in situations other than the classical one beneath the seat of an outdoor privy.

The diagnosis was made with little difficulty in these cases, no other condition being even suggested in most of the more recent instances, even in the absence of a history of seeing the

TABLE V
Incidence of Poisonous Spider Bites
By Months

January	0
February	0
March	2
April	3
May	5
June	6
July	9
August	13
September	8
October	8
November	3
December	3
Total	60

TABLE VI
Diurnal Incidence of Arachnidism

A.M.	12- 1	2	P.M.	12- 1	2
	1- 2	0		1- 2	0
	2- 3	0		2- 3	0
	3- 4	2		3- 4	2
	4- 5	0		4- 5	4
	5- 6	1		5- 6	2
	6- 7	4		6- 7	2
	7- 8	2		7- 8	4
	8- 9	1		8- 9	6
	9-10	4		9-10	5
	10-11	2		10-11	2
	11-12	3		11-12	4
No record		6	Total		60

spider, but in the earlier cases various abdominal conditions, ruptured gastric or duodenal ulcers, appendicitis with peritonitis, or renal or biliary colic were repeatedly suggested, as well as tabetic crises, food poisoning, pleurisy or pneumonia, and tetanus. Local infections with cellulitis or lymphangitis supervened in four instances.

Differential Diagnosis

The diagnosis of arachnidism due to the bite of the *Latrodectus mactans* spider depends upon:

1. A history of exposure to, or actual experience of, the bite of the black spider. There is usually little or no visible lesion at the site of the bite.

2. Pain, starting usually in the region of the bite but not always, and spreading until most of the larger groups of muscles of the body are involved. Except in multiparous women, the pain is usually felt most intensely in the abdominal muscles. The pain increases, reaching its maximum about an hour after the bite, and is then evidently excruciating and agonizing, usually continuous but occasionally cramp-like or intermittent and manifested by writhing, doubling up and screaming or moaning.

3. Rigidity and muscle spasm, most notable in the muscles of the abdominal wall, which become board-like and hard, as in general peritonitis. It should be noted, however, that the rigidity is not confined to the abdomen, but that the intercostal muscles may contract, causing a "tightness" of the chest, and the back muscles may contract, causing a backache or stiffness of the back. The spasm of the calf muscles and other muscles of the extremities may be remarked, and the legs may be drawn up on the abdomen. True local tenderness, however, is usually entirely absent, or disproportionately slight compared to the intensity of the muscle spasm.

4. Increased blood pressure, usually 20 to 40 mm. above the normal for that patient, hyperactive reflexes, especially the knee jerk, and an increase in the pressure of the spinal fluid are usually present.

5. A mild rise of body temperature, with occasionally, but not uniformly, a slow pulse, and a definite leucocytosis, with an increased percentage of polymorphonuclear leucocytes and a shift to the left in the Schilling count is to be expected.

6. Profuse perspiration, restlessness and anxiety, tossing about in agony and similar symptoms are usually seen. Nausea and vomiting, localized edema, twitching or spasms of the muscles of the extremities, and priapism and urinary retention are occasionally noted.

If these considerations are borne in mind, it is not usually difficult to distinguish a case of arachnidism from one of an acute surgical abdominal condition, renal or biliary colic, tabetic crises, food poisoning, pneumonia or pleurisy, tetanus, or any of the other conditions that may be suggested.

Poisonous spider bites could be, to a great extent, avoided if the general population were taught that these small and innocuous looking creatures are really dangerous and should not be tolerated in the vicinity of human beings. In order to avoid the unnecessary extermination of the many useful and desirable species of spiders,

the characteristics of this species should be made known and the peculiarities of its web popularized so that it may be readily recognized whenever encountered. This web consists of straggly, uneven, coarse viscous threads running in all directions in all three dimensions, with none of the geometrical exactitude which gives to the orbweavers or sheetweavers their esthetic charm. The poisonous female *Latrodectus mactans* may stretch its slim glossy black legs over as much as two inches spread. The under surface of the black globular abdomen usually bears a bright red patch shaped somewhat like an hourglass. Once seen it is readily identified. Methods of extermination of the spider include destruction of its web and egg sacs, as well as the spiders themselves, with a broom, shoe, fly swatter or any other solid object available, or by the use of fly sprays or other special poison sprays, and by the encouragement of the natural enemies of the spider, both insects and birds.

Palliative treatment to alleviate the acute pains of spider bite poisoning is always sought, but usually is only partially effective. Opiates were given to most of our patients, but remark is repeatedly made of their relative inefficiency in this condition. Other sedatives and anodynes, including bromides, barbituric acid derivatives, and other coal tar compounds, were also used. The employment of hydrotherapy, in the form of hot baths, hot compresses and other applications, appeared to give considerable relief in many cases. Spinal puncture was performed only in a half-dozen cases, but the immediate relief following it in most of these instances was so striking that it must be accorded special consideration as a therapeutic measure in this condition. The intravenous injection of a ten per cent solution of magnesium sulphate was given in one instance, with some apparent relief in symptoms.

Blood was taken from about one-third of these patients from one to ten weeks after the bite, and the serum was given to twenty-four patients soon after admission to the hospital. In three instances the treatment was repeated. The doses varied from two to thirty-five c.c. of this convalescent serum, given intramuscularly. It was administered from two to twenty-two hours after the bite was sustained, the average time being eight hours. The clinicians repeatedly reported that substantial relief from the symptoms followed soon after its administration.

The results of serum therapy in arachnidism are not readily evaluated, because of the variability of the symptoms and the fact that the milder cases might be expected to be more apt to escape this treatment. Analysis of the data available shows that the average

TABLE VII
Interval Between Bite and Onset of Pain

	CONVALESCENT SERUM		TOTAL
	TREATED	UNTREATED	
"Immediate"	8	9	17
"Soon"	4	4	8
0-15 min.	2	3	5
15-30 min.	4	2	6
30-60 min.	2	1	3
60 min.-	1	2	3
No record	3	15	18
Total	24	36	60

TABLE VIII
Interval Between Bite and Most Severe Pain

	CONVALESCENT SERUM		TOTAL
	TREATED	UNTREATED	
0-30 min.	3	3	6
30-60 min.	2	4	6
1- 2 hours	5	6	11
2- 3 hours	2	2	4
3- 6 hours	3	4	7
6 hours-	1	2	3
No record	8	15	23
Total	24	36	60

time of development of the symptoms was practically the same in those receiving the serum from those not so treated, and that the first signs of subsidence of the symptoms appeared after approximately the same interval of time. In the patients who received the serum treatment within eight hours of the bite, the main relief was obtained several hours earlier than in those not so treated, and complete cessation of symptoms and the recovery from after-effects was somewhat more rapid in the treated group than in those receiving no such treatment.

Nevertheless, just as many clinicians feel that they can well dispense with the use of the antitoxic serum in the ordinary case of scarlet fever, potent and specific as this treatment is acknowledged to be, so it is thought that the convalescent serum in arachnidism, although theoretically correct and practically of apparent clinical value, is not an essential requisite in handling most cases of spider bite poisoning.

Perhaps it should be stated that despite its severe symptoms, spider bite poisoning is, in the majority of cases, a self-limited condition, and generally clears up spontaneously within a few days. Much suffering and even fatalities are due to injudicious treatment rather than to the venom itself. Thus, stimulants, caffeine, strychnine, adrenalin, and especially the lavish use of alcohol have no ra-

TABLE IX
First Relief from Pain

HOURS UNTIL FIRST SIGN OF RELIEF	CONVALESCENT SERUM		UNTREATED	TOTAL
	TREATED IN FIRST 8 HRS.	TREATED AFTER 8 HRS.		
1	0	0	2	2
2	0	0	1	1
3	1	0	2	3
4	0	0	2	2
5	2	1	3	6
6	1	1	3	5
7	1	0	0	1
8	1	0	1	2
9	0	0	0	0
10	1	0	2	3
11	0	0	0	0
12	0	2	1	3
No record	5	8	19	32
Total	12	12	36	60

TABLE X
Main Relief from Pain

HOURS UNTIL MAIN RELIEF	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	IN FIRST 8 HRS.	AFTER 8 HRS.		
1- 6	1	0	0	1
6-12	2	0	3	5
12-18	5	4	7	16
18-24	1	2	6	9
24 hrs.-	2	6	10	18
No record	1	0	10	11
Total	12	12	36	60

TABLE XI
Complete Recovery from Pain

DAYS UNTIL COMPLETE SUBSIDENCE	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	IN FIRST 8 HRS.	AFTER 8 HRS.		
0-1	1	2	3	6
1-2	2	2	3	7
2-3	4	2	5	11
3-4	1	5	2	8
4-5	0	0	4	4
5-6	0	0	3	3
6-	0	0	4	4
No record	4	1	12	17
Total	12	12	36	60

TABLE XII
Duration of Hospital Stay

DAYS IN HOSPITAL	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	FIRST 8 HRS.	AFTER 8 HRS.		
0- 1	1	0	1	2
1- 2	3	0	7	10
2- 3	3	1	9	13
3- 4	1	4	4	9
4- 5	3	3	3	9
5- 6	1	2	4	7
6- 7	0	1	3	4
7-	0	1	5	6
Total	12	12	36	60

tional indication and are probably productive of more harm than good in this condition. Similarly, local treatment by incision, caustic chemicals, and even the actual cautery, is practically always too late to be of any value since the venom is so rapidly absorbed that systemic effects develop within a few minutes and generally reach their acme within an hour after the bite. On the other hand, such treatment is apt to open the way to local infection, since the spider usually lives in dirt and filth and the site of the wound is apt to be contaminated with germs. Since there is little or no local lesion, the simple application of any mild antiseptic, such as tincture of iodine, is preferable. The fact that four of our cases of spider bite poisoning thereafter developed local infections at the site of the bite, and others have reported deaths from similar infections, emphasizes the desirability of such local antiseptic application.

Conclusions

The black widow spider is found over more than half of the United States. Nearly four hundred instances of systemic poisoning from its bite have been reported. Unnecessary operations upon such patients could be avoided if all physicians recognized that an acute condition with rigidity of the abdomen, fever and leucocytosis, and occasionally nausea and vomiting, may supervene as a result of the bite of a black spider. It may be differentiated, however, from acute abdominal lesions requiring surgical intervention by the presence of spasm in muscles other than those of the abdomen, by the absence of marked local abdominal tenderness, and by the concomitant rise in the pressure of the blood and spinal fluid. The mortality rate is low and patients usually recover spontaneously within a few ways, but the suffering is intense and more than a dozen fatalities have been reported. Sixty patients have been treated at the Los Angeles General Hospital with no deaths.

The prevention of arachnidism depends upon popular education as to the danger of these spiders and the advisability of their eradication. Local treatment of the bites should consist of simple antiseptic applications, and additional trauma by incisions, cauterization, or the injection of hypothetical antidotes should be avoided. Stimulation and alcoholic drinks are usually contraindicated. Harmful surgery may be obviated by correct diagnosis. Opiates and hypnotic drugs may be used as palliative measures, together with sedative hydrotherapy and the reduction of intracranial pressure by the administration of hypertonic solutions or spinal puncture. Specific treatment with serum from convalescent victims is of value, particularly if administered early.

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Studies on a Urinary Proteose

II. Skin Reactions and Therapeutic Applications in Hay Fever

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THE literature prior to 1919 dealing with the antigenic properties of protein cleavage products has been thoroughly reviewed by Fink.[1] He briefly summarizes the numerous papers reviewed by stating that experiments with products of protein digestion show that proteins cannot be disintegrated much, if any, beyond the coagulable form without losing their sensitizing properties. By experiments in which he prepared proteoses from egg albumin he demonstrated that proteoses have definite antigenic properties. Auld,[2] in 1917, began to advocate the use of nonspecific peptone therapy in the treatment of bronchial asthma and since that time he has published numerous papers on various phases of its use. He uses the word "peptone" advisedly in that it represents a mixture of proteoses and peptones and he recommends Armour's peptone solution because of its high proteose content.[3] Many other investigators have used peptone solutions in one way or another for nonspecific desensitization in the various allergic conditions.[4, 5, 6, 7, 8] Vallery-Radot and Giroud[9] have used Witte's peptone solution intradermally in the treatment of hay fever.

The presence of proteose in the urine excreted during suppurative and febrile conditions, malignancy, and tuberculosis has long been recognized.[10] The significance of this observation was not definitely understood although Wells mentions the possibility that the symptoms in these conditions may be due in part to proteose intoxication. In 1928 Barber and Oriel[11] began to publish observations regarding the appearance of a proteose in the urine excreted during allergic conditions as well as in those just noted. These investigators found the presence of the proteose to be the cause of a so-called "ether reaction" which was obtained as a result of extracting urine excreted during allergic symptoms with ether after previously acidulating with sulphuric acid. A positive reaction consisted in the appearance of a waxy scum in the ethereal layer beneath the superficial froth. In strongly positive tests the tube of urine could be inverted without spilling. The more acute the allergic symptoms, the more positive the test. They were able to ob-

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tain a precipitate from the ethereal layer by adding an excess of alcohol. Aqueous solutions of this precipitate gave the characteristic chemical tests for proteoses. The clinical significance of this urinary substance has been further investigated by Oriel[12, 13, 14] and by Oriel and Barber.[15] After careful observation and well controlled experimentation they have demonstrated the following in the allergic patient: If the proteose is prepared from urine collected during a period when symptoms are present, his skin will usually respond with characteristic wheal formation after intradermal injection, reinjection will reproduce his allergic symptoms, and desensitization will usually result in an improvement or disappearance of his symptoms; if the proteose is prepared from urine collected when symptoms are not present, none of these phenomena will take place.

We have studied this proteose sensitivity in a variety of conditions[16, 17] but this paper will deal exclusively with a series of hay fever patients treated during the spring and summer of 1931.

Proteose prepared according to the methods of Oriel and Barber[15] was used as follows for skin testing: Tests were performed upon the volar surface of the forearm beginning with the control (1 c.c. N/10 sodium hydroxide in 9 c.c. of Coca's solution) just distal to the crease of the elbow. Below this the proteose dilutions were injected intradermally in the order of their strength at distances of 3 cm. from each other. About 0.05 c.c. of solution was used for each injection. A positive skin reaction is characterized by the development of a wheal within from 5 to 10 minutes, from the edges of which one or more pseudopods develop (see figures 1 and 2). At the height of its development, which usually takes place in from 15 to 30 minutes, the wheal is circumscribed by a scarlet flare. The patient sometimes complains of itching. The wheal gradually subsides leaving an erythematous blotch which may not disappear for several hours. In a few instances, especially in the hay fever patients, this area of erythema has gradually increased in size up to 12 hours and has been accompanied by tenderness and a sense of heat. In very sensitive patients, especially those subject to asthma, we have found that a focal reaction may follow either the intradermal test or the subcutaneous injection of too large a dose. Consequently it should be stated that for the past few months we have been resorting to the scratch method of testing for sensitivity in order to avoid untoward reactions. For this purpose we apply a few drops of the N/10 sodium hydroxide-proteose solution to a scratch upon the volar surface of the forearm using N/10 sodium hydroxide as a control.

The initial dosage for desensitization is best arrived at by selecting the dilution next below that which gives the least positive intradermal reaction. The first dose is usually 0.05 c.c. subcutaneously. Injections are given at from three to four day intervals and the dose is gradually increased or decreased as indicated by the patient's clinical progress. In our experience no focal reactions have developed if desensitization were started with the

weak dilution as indicated. If a focal reaction does occur, the next weaker dilution should be used.

The group of hay fever cases herein presented represents one of the numerous allergic conditions in which we have studied the proteose reactivity. In all we have investigated the proteose sensitivity in over 100 patients including, aside from hay fever, such conditions as asthma, serum sickness, eczema, erythema multiforme, migraine and rheumatoid arthritis. Of these we have found hay fever and eczema the most prompt to yield to proteose desensitization. We feel that the presentation of this series of hay fever cases should be of interest because of the very suggestive results obtained and also because of its possible bearing on the study and therapeutics of allergic diseases.

Case I. Male, age 17. Onset of hay fever in early summer. Sensitive to orchard grass, timothy, June grass, lambs' quarter, kochia, pigweed, pasture sage, and false ragweed. This patient was studied merely as a matter of interest to see if proteose prepared from a case of hay fever would induce a positive intradermal reaction. The test proved to be a plus 2.* Treatment with the proteose was not attempted.

Case II. Male, age 21. Onset in early summer. Sensitive to various grasses and giant ragweed. Given pollen injections for hay fever during the previous season with no results. Intradermal proteose test, plus 2. Given proteose injections at biweekly intervals with immediate and complete relief of symptoms. After three weeks the patient moved to Michigan, proteose injections were stopped, and the hay fever returned.

Case III. Female, age 29. Onset in early summer. Sensitive to June grass, timothy, orchard grass, lambs' quarter and kochia. Intradermal proteose test, plus 2. Previous pollen desensitization with only fair results. After two injections the symptoms entirely cleared and the patient did not return for further treatment.

Case IV. Female, age 30. Onset in early summer. Sensitive to pasture sage, orchard grass, Russian thistle, broad and narrow leaf cottonwood, pigweed and indian hair tonic. Treated during previous seasons with pollen injections with slight relief and was taking pollen at the time proteose was prepared. Intradermal proteose reaction, plus 3. Proteose administration was started in conjunction with the pollen desensitization with the result that added relief was obtained although hay fever still persisted to a mild degree.

Case V. Female, age 29. Onset in early summer. Sensitive to pigweed, kochia, Russian thistle and lambs' quarter. Pollen injections during the past season with good results. Had frequent attacks of urticaria which became aggravated during hay fever season. A proteose was prepared in March for the urticaria to which she was skin sensitive and from the administration of which she derived some benefit. With the onset of hay fever another proteose was prepared to which she gave a marked intradermal reaction. After the administration of the proteose the hay fever would improve but as the dosage was increased the urticaria would become more pronounced. Consequently the treatment of this particular case was not entirely satisfactory.

Case VI. Female, age 8. Onset in early summer. Complicated by asthma during the previous season. Skin tests for pollen sensitivity not done. The intradermal proteose test was violent in that erythema persisted for over 12 hours. Following proteose administration the symptoms cleared completely and there was no recurrence of her asthma.

Case VII. Female, age 39. Onset in early summer. Complicated by asthma during previous season. Sensitive to green sage, pasture sage, pigweed, Russian thistle and indian hair tonic. Received pollen injections the year before with only slight relief of hay fever; asthma recurred as

*plus 2=moderate reaction; plus 3=marked reaction; plus 4 = very marked reaction.

usual. Intradermal proteose reaction was plus 4, and was followed after two hours by an aggravation of the symptoms. Proteose desensitization resulted in considerable relief and the asthma was practically absent as compared with the previous year. In August the hay fever became somewhat worse. Although it was possible that certain of the weeds were responsible for this aggravation another proteose was not prepared.

Case VIII. Female, age 39. Onset in early summer. Possible pollens concerned in the etiology not determined. Intradermal reaction to proteose was plus 3, and following the test there was an increase in the nasal discharge. Desensitization with the proteose resulted in a great improvement; the patient suffering only an occasional attack.

Case IX. Female, age 17. Onset in early summer. Complicated by chronic sinusitis. Sensitive to many of the grasses and to Russian thistle. Desensitization with pollens gave no relief in 1928, 1929 or 1930. Intradermal reaction to proteose, plus 3. Relief from desensitization was complete for one month and a half (the middle of August) when mild symptoms returned. A second proteose solution was not prepared.

Case X. Male, age 45. Onset in early summer. Sensitization tests for the pollens not done. Intradermal reaction to proteose, plus 3. Relief from desensitization was considerable though not complete.

Case XI. Female, age 35. Onset in early summer. Complicated by acne. Pollen sensitization tests had been performed before but results were not known to the patient. Previous desensitization gave no relief. Intradermal proteose reaction was plus 4, the erythema increasing up to 12 hours. Relief after desensitization was complete and it was also of interest to note that the acne cleared completely and there was improvement in the general condition.

Case XII. Female, age 33. Onset in late summer. Pollen desensitization every year since 1925 gave good results. Intradermal proteose reaction, plus 3. Complete relief obtained after proteose desensitization.

Case XIII. Male, age 52. Onset of symptoms in late summer. No information as to pollen tests or previous treatment. Intradermal proteose reaction was plus 4. Marked relief obtained following proteose desensitization.

The most important features concerning this series of cases are summarized in the accompanying table.

It has been recognized that only certain organs of the body may exhibit allergic manifestations. Bronchial musculature or nasal mucous membrane may be sensitive to a given antigen while the skin may or may not show an allergic response.

Alexander[18] reviews this matter quite completely and points out that while the skin test is not always of much help in such conditions as asthma, urticaria and eczema, it is quite reliable in hay fever (between 90 and 95 per cent of the cases). None of our hay fever cases gave a negative or questionable dermal reaction. The standards for the interpretation of the intradermal test must, of course, be arbitrary. We interpret the responses as slight, moderate, marked and very marked, or plus, plus 2, plus 3, and plus 4, respectively. Reference to figures 1 and 2 will afford an idea as to our standards for judging the degree of reaction. Figure 1 exemplifies a marked (plus 3) and figure 2 a very marked reaction (plus 4). Focal reactions consisting in an aggravation of symptoms occurred in cases V, VII, VIII, and XII subsequent to the intradermal test. While no asthmatic attacks were induced the possibility of their occurrence must not be overlooked, and since constitutional reactions may assume serious proportions it should be stated again that we have decided to abandon the intra-

Summary of Results Obtained by Proteose Desensitization in Hay Fever

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Obtained by Proteose Desensitization in Hay Fever

Case No	Intradermal Reaction	Focal Reaction	Onset of Hay Fever	Time under our observation	Interval for therapeutic responses	Degree of relief obtained	Miscellaneous
I	2 plus	0	Early				
II	2 plus	0	Early	3 weeks	24 hours	Complete	To Michigan where symptoms returned.
III	2 plus	0	Early	3 months	24 hours	Complete	Received only 2 proteose Injections.
IV	3 plus	0	Early	2 months	2 weeks	Partial	Pollens given simultaneously. Proteose gave added relief.
V	3 plus	+	Early	4 months	1 week	Partial	Complicated by urticaria. One improved at expense of other.
VI	4 plus	0	Early	4 months	1 week	Complete	Asthma previous summer. No asthma after proteose desensitization.
VII	4 plus	+	Early	2 months	1 week	Partial	Very little asthma as compared to the year before.
VIII	3 plus	+	Early	1 month	1 week	Partial	
IX	3 plus	0	Early	3 months	1 week	Complete until August	Symptoms returned in mid-August.
X	3 plus	0	Early	2 months	1 week	Almost Complete	
XI	4 plus	0	Early	3 months	24 hours	Complete	Acne cleared. Improvement in general condition.
XII	3 plus	+	Late	6 weeks	1 week	Complete	
XIII	4 plus	0	Late	6 weeks	1 week	Almost Complete	

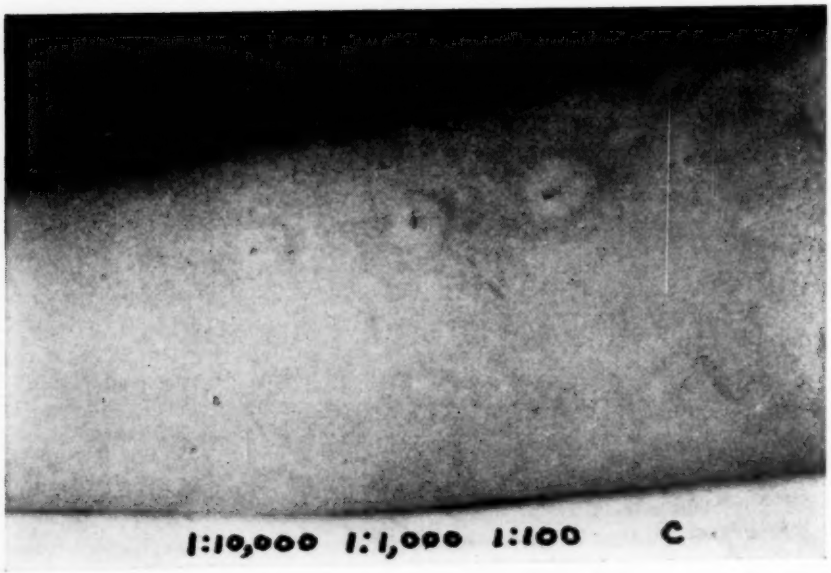

FIG. 1. Case VI. Intradermal reaction at 15 minutes. Interpreted as plus 4.

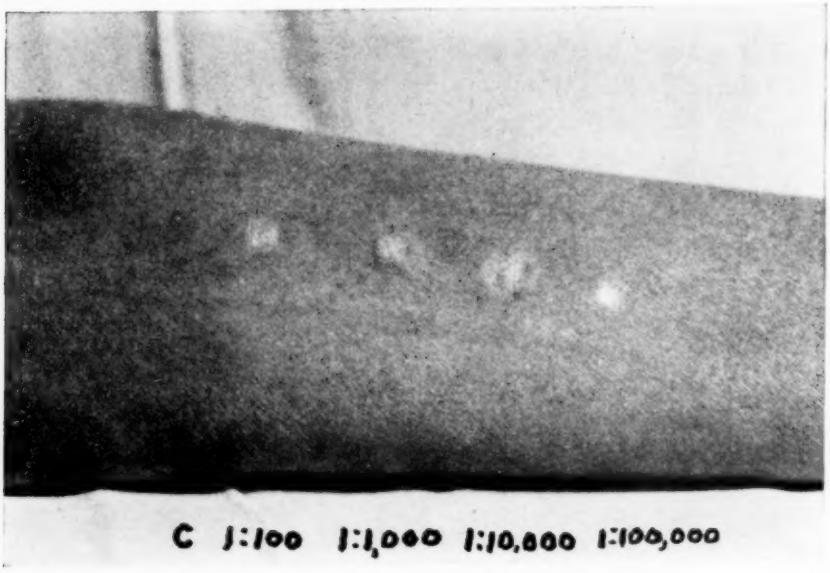

FIG. 2. Case VIII. Intradermal reaction at 15 minutes. Interpreted as plus 3.

dermal test in favor of the scratch method.

Eleven of the thirteen cases were of the early type of hay fever; two of the late. Where pollen desensitization is attempted the best results are obtained with the early type. Our results do not prohibit the assumption that proteose desensitization would be any less effective in the late than in the early types. The results obtained from pollen desensitization vary somewhat and depend to a certain degree upon the experience and skill of the physician administering the treatment. Thommen,[19] after reviewing the reports of various investigators, gives average results obtained as follows: complete relief 10 to 30 per cent; almost complete relief 24 to 40 per cent; partial relief 20 to 30 per cent; and no relief 9 to 12 per cent. The results obtained from proteose desensitization compare very favorably with those ordinarily obtained following pollen administration. In comparing the results obtained from the two types of therapy it must be remembered that in order to obtain the most satisfactory response to pollen desensitization the patient must be under treatment for from two to three months before the onset of the hay fever is expected. Pollen treatment instituted after the onset of symptoms is frequently unsatisfactory. On the other hand proteose therapy is of value only after symptoms appear. In view of this consideration we feel that the use of the patient's proteose should be a distinct and valuable aid in the management of hay fever.

Furthermore, it is very likely that the use of proteose in the late type of hay fever would make it possible for a greater number of patients to obtain relief. Case IV suggests another possible use for proteose. This patient received the preseasonal pollen injections for several weeks. When the trees and grasses began to pollinate her symptoms of hay fever appeared. At that time proteose therapy was instituted as a complementary measure. Under this regime, although the symptoms did not entirely clear, she felt that she had obtained definite additional relief. The reason for this added relief may be that the patient was sensitive to pollens which were not included in treatment initiated earlier in the spring. Cases VII and IX obtained great relief early in the summer, but with the pollination of the weeds later in the season the hay fever returned. The observations made in these cases strongly suggest a specific relationship between the various pollens and their corresponding proteoses. Cases V and XI presented certain other very interesting points relative to the specificity of the urinary proteose. Case V was complicated by urticaria which had been present for some time prior to the onset of hay fever. It is probable that proteose prepared after the onset of hay fever had antigenic substances present which were also associated with the urticaria. Since a dosage that seemed to cause improvement in the hay fever appeared to aggravate the urticaria, it is assumed that the respective antigenic substances were specifically related to the two conditions and that they were present in conflicting concentrations which precluded the attainment of satisfactory

results. On the other hand Case XI demonstrated quite the opposite in so far as results were concerned. The patient had had acne for years. Desensitization resulted in complete relief of both and to date (March, 1932) the acne has not returned. It is also of interest to note that her general condition has greatly improved. Here again it is to be assumed that antigens were obtained in the proteose which were concerned in the production of acne as well as hay fever.

Conclusions such as these strongly support the contention that desensitization with the allergic patient's own proteose is based upon the principles of specific therapy.

The use of nonspecific protein desensitization in an effort to counteract reactivity to specific proteins has undoubtedly played a most important rôle in the treatment of allergic disease. Auld[20] has recently advocated the use of a special "serum peptone" which is partially prepared from the patient's own blood. If a normal individual eats eggs 48 hours after being injected intracutaneously with serum from an egg sensitive patient, a wheal will develop at the site of the injection. This is a variation of the Prausnitz-Küstner reaction and demonstrates the fact that specific antigenic substances are circulating in the blood stream. If this is true, they must be present to a certain extent in the peptone which Auld describes. From the same standpoint the use of auto-hemo-therapy as advocated by Kahn and Emsheimer,[21] Henske[22] and Ghosal[23] is also in part specific in its principle. Flandin[24] strongly advocates intradermal injections of the patient's own serum in the treatment of hay fever. If the antigens concerned in the production of allergic symptoms are circulating in the blood they should no doubt be eliminated through the kidneys as well as through other channels. Duncan[25, 26] in 1912 and 1914 advocated the oral administration of the patient's own urine in certain diseases, basing his treatment upon the belief that certain bacterial and tissue toxic substances were eliminated through the kidneys and that ingestion of these would stimulate specific antibody formation. Two cases in which the patients claim to have been relieved from asthmatic paroxysms by drinking their own urine have come to our attention. While desensitization by the oral route is of doubtful value it is of interest to note that Thommen[27] believes he has induced relief in a case of hay fever following the oral administration of ragweed pollen in large doses.

The work of Oriel and Barber[15] demonstrates quite conclusively that the antigenic substances which they have recovered from the urine of allergic patients are specifically related to the antigens primarily responsible for the symptoms. Proteose obtained from a case of serum sickness will stimulate wheal formation when injected intradermally in other individuals known to be sensitive to horse serum. They showed further that the proteose from a case of serum sickness would induce asthma when administered subcutaneously in rather large dosage to a "horse-asthmatic". By the use of the Prausnitz-Küstner reaction Barber and Oriel advance further evidence as to the specific nature of the urinary proteose. Serum

from an individual suffering from serum sickness was injected intradermally at two points in a normal individual. Twenty-four hours later proteose prepared from this case of serum sickness was injected intradermally in one of these areas and proteose prepared from a non-serum sensitive individual was similarly injected in the other. A positive reaction as evidenced by wheal formation appeared in the area injected with serum proteose, no reaction occurring in the second or control area. Oriel[14] using the uterus of a guinea pig which he had sensitized with proteose prepared from a milk sensitive patient observed a strong contraction when milk was added to the perfusing fluid in which the uterus was suspended. Similar results were obtained with a uterus sensitized to milk when the proteose was added to the perfusate.

Many of our observations substantiate these findings. One of our patients presented a violent generalized urticaria following the ingestion of a breakfast food containing flax to which she was found to be sensitive. Proteose was prepared from this patient and tested in another patient known to be flax sensitive. A marked local reaction was obtained. Similar reactions were observed when proteose prepared from a case of serum sickness was tested intradermally in serum sensitive individuals. Two hay fever patients each sensitive to the same pollen will respond with positive intradermal tests to each other's proteose.

The significance and exact origin of this urinary antigenic substance is somewhat problematical. Early workers in the field of immunology recognized the possibility that the symptoms of anaphylaxis might be due to products of parenteral digestion or to products formed as a result of the reaction between the primary antigen and the sensitized tissue. Oriel and Barber[15] after reviewing the experimental work of Lewis, Dale and Manwaring, consider that the urinary proteoses which they have found in all probability consist of these "secondary antigens" which are formed as a result of the interaction between the "primary antigens" and the sensitized tissues of the body.

Regardless of the origin of this antigenic substance found in the urine of allergic patients it is evident from the results reported by the original investigators and also from the hay fever cases reported in this paper that desensitization with homologous urinary proteose is of great practical importance. Many cases of allergy are seen in which the primary antigen is obscure and if a patient can be desensitized with his own proteose much is to be gained. Other cases occur in which it is probable that the primary antigen is derived from metabolic processes, or as the result of low grade infections, and in such cases it is difficult to desensitize a patient by the usual methods.

It must be understood that further investigation and experience with this urinary substance is necessary in order to arrive at a better understanding regarding its origin, significance, and technique of application. We feel that the work of Oriel and Barber is of great importance in that it may open the way toward the solution of many problems of an allergic nature.

Conclusions

The literature regarding the antigenic properties and uses of proteoses is briefly reviewed laying particular stress upon the work of Oriel and Barber.

Urinary proteose was prepared according to the original methods of these investigators and the intradermal and therapeutic response determined in twelve cases of seasonal hay fever. All cases gave positive intradermal reactions to their respective proteoses and improved after desensitization.

These cases are discussed at length regarding the clinical results obtained and also regarding the contention that a given proteose is specifically related to a given antigen. The work of Oriel and Barber is briefly discussed relative to this point and confirmatory observations by us are indicated.

The probable origin and significance of this urinary substance is also mentioned in an effort to point out the important rôle which it may play in the future study and treatment of allergic diseases.

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The Successful Treatment of Hay Fever and Pollen Asthma

By Alexander Sterling, M.D., *Philadelphia, Pa.*

DESENSITIZATION with pollen extracts for hay fever patients has been in vogue for the last fifteen years. The method originally conceived by Walker, Cooke, and others has not changed a great deal over that period and even now the treatment by the general practitioner of patients with hay fever and hay fever and asthma consists of a series of fifteen injections at weekly intervals. There has been so much controversy regarding beginning and protective doses, types of doses, etc., that there scarcely seems a way for the general practitioner to determine preference for any of the so-called "treatment sets" now on the market. Of these various "sets", there are many which are similar in contents and which are alike in that they are successful in only twenty per cent of all hay fever patients. Physicians and patients alike have informed me that pollen desensitization is of no avail, because they have tried this, that, and the other manufactured product with no success. The complainings have reached the stage where the practitioner says that there is no relief for hay fever, and at times insists that these "treatment sets" cause an even worse condition in the patient.

It is unfortunate that from the very beginning of pollen therapy there was no standard for the preparation of pollen extracts nor any standard treatment adopted by allergic societies and recommended to pharmaceutical houses. The conditions existing, which I would like to explain and attempt to solve, are several.

First, there is no standardization in product of the various numerous pollen extracts now available. The pollen extracts are obtained from menstruums of saline, alcoholic saline, glycerol saline, and other types. All sorts of percentage compositions are resorted to in the make-up of the menstruums. I have experimented with various types and have found that if the pollen is extracted from a menstruum of fifty per cent glycerin and fifty per cent buffered salt solution, nearly perfect results are obtainable. All menstruums which do not contain glycerin are unstable. They are potent only when freshly prepared, when constantly kept on ice, or when received from the manufacturers. They quickly lose potency with changes in temperature or after certain intervals of time. These results are not dependent entirely upon the extraction liquid. Another fault existing in the makeup of the various pollen extract is in the standard of measurement. The various units used

to grade the strengths of pollen extracts range from protein nitrogen units (each unit equivalent to 0.001 mg. of protein nitrogen) to pollen grain units (the amount of pollen grain extract from 0.001 mg. of pollen).

Second and most important, no preparation on the market has sufficient material made up in a proper way for correct desensitization and successful results. It would be rather illuminating at this time to examine several of the products now in common usage.

Product number 1 contains three 4 c.c. vials of extracts of various pollens of particular groups. The three vials contain various proportions of pollen grains per cubic centimeter and furnish sufficient material for the usual fifteen dose treatment. The course of injection treatment is so constituted that the dosage begins with two pollen units, and the protective dose furnished is 1200 pollen grain units. A higher concentration is available in a 4 c.c. vial containing 2000 pollen grain units per cubic centimeter.

Product number 2 is a mixture of various pollen extracts standardized to contain about 2000 pollen grain units, or 500 protein nitrogen units per c.c. The extract is supplied in 5 c.c. vials and it is suggested that the practitioner adopt a graduated dosage beginning with 1/20 c.c., and progressing in either twentieths or tenths of a c.c. so as to obtain thirteen injections from the 5 c.c. vial. A fifteen dose treatment package of graded doses proceeding from 100 pollen grain units to the protective dose of 4000 pollen grain units is also manufactured. Each dose is in a separate syringe.

Product number 3 is standardized according to the "protein nitrogen unit". This product is in two 5 c.c. vials; the starting dose is 5 units and the highest dose is 100 units. Sixteen doses are offered for injections and if larger doses are required another vial is offered, the highest dose being 250 protein nitrogen units.

Product number 4 contains four 3 c.c. vials and one 1 c.c. vial. It is an alcoholic saline pollen extract ranging in dilutions (volumetric method) from 1/10,000 to 1/100. The highest dose suggested is 5 minims of 1:100 dilution. Similar products are manufactured by other well known firms. They are all proponents of "treatment sets".

The doses, as can be seen from the above, range from between 2 pollen grain units and 100 pollen grain units as the lower level, to the apparently highest protective doses of from 1000 to 4000 pollen grain units. In a single exceptional case only does the highest protective dose reach anywhere near the correct figure of 10,000 pollen grain units. The highest dose suggested by the pharmaceutical houses is between 3 and 5 minims of a one per cent solution (or 0.025 or 0.030 nitrogen units), which they consider sufficiently protective.

For several years I have had five groups of 10 patients, each of whom I have treated with various advertised treatment sets. Only twenty per cent of these patients were benefited. Furthermore, only those who had hay fever were benefited. Those who had hay fever and asthma were not relieved by these preparations. Not until I began to use a three per cent concentrated pollen extract in various dilutions did I achieve nearly perfect re-

sults in 90 to 95 per cent of patients.

Standardization of pollen extract, as mentioned above, by the protein nitrogen unit does not hold good for the reason that it has been proved by investigators that the carbohydrate fraction of pollen is just as responsible in the production of hay fever and asthma symptoms as the nitrogen fraction. I therefore have selected the pollen grain unit which is the quantity of pollen weight per unit of diluent. For example, 3 gms. of pure washed pollen to 100 c.c. of glycerol and buffered salt solution is passed through a Berkefeld filter after one or two days standing. This extract contains approximately 30,000 to 32,000 pollen grain units per 1 c.c. which is a three per cent concentrated pollen extract. The reason why I limit myself to a three per cent pollen extract is that it has been demonstrated by many investigators that a three per cent concentrated pollen extract is equivalent to a saturated solution of pollen.

I use the following *dilutions*:

Dilution No. 1. Five minims of 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. Each minim containing 57 pollen grain units. (The diluent that I favor is a sterile physiological salt solution containing 0.2 or 0.3 per cent carbolic acid). I find from my experience that any solution which contains from 30 to 50 per cent glycerin is very painful when injected.

Dilution No. 2. Ten minims of 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. Each minim containing 114 pollen grain units.

Dilution No. 3. Twenty minims of a 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. Each minim containing 228 pollen grain units.

Dilution No. 4. Forty minims of 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. Each minim containing 456 pollen grain units.

Dilution No. 5. Eighty minims (5 c.c.) of 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. Each minim containing 912 pollen grain units.

Treatment. The most important factor in this work is to begin treatment with a dose small enough to give a local reaction not exceeding one inch (from 2 to 2.5 cms.) in diameter. Quite often I find that the 2 minim dose of dilution 1 gives quite a large local reaction, sometimes accompanied by a constitutional reaction. In those cases I am compelled to make another dilution (1 A) containing about 2.5 minims of 3 per cent concentrated pollen glycerol extract to 10 c.c. diluent. This dilution contains about 28 pollen grain units. The first injection may even go down as low as 14 pollen grain units, in order to obtain a local reaction not exceeding one inch in diameter. It is here, in the beginning of treatment, that the only difference between a strongly sensitive and a weakly sensitive patient's dosage occurs. There is no necessity for complicating the treatment with various classifications of sensitivity A, B, C, and D as it is being practiced in some clinics. The protection doses in all cases are approximately the same.

Having obtained the starting dose (that which produces a local reaction not exceeding one inch in diameter) whether it be in solution 1, 1A, or 1B, the next dosage is four minims of that

solution. The dosage of dilutions 1, 2, 3, and 4, is gradually increased consecutively to 4, 6, 8, 10 and 12 minims. When changing from one solution to the next the first dose of the next vial may be 4, 5, or 6 minims. The reason why I start with four minims of the following dilutions (which is a repetition of the dose) is to prevent a reaction from too large a dose from the next vial in case of difference or freshness of the pollen extract. When the dose reaches solution 5, (which is approximately 1 per cent concentrated pollen extract), injections increase 1 minim daily until 12 to 15 minims are reached before the pollination periods of the respective seasons. That, in the majority of cases, furnishes the highest protective dose.

A suggestion of all pharmaceutical houses is that injections should cease with the beginning of the season. That is faulty. The patient should receive injections of the highest protective dose (from 12 to 15 minims of 1 per cent pollen extract) throughout the season at least once a week. In severe seasons, at the slightest appearance of mild symptoms my patients receive injections every day for a few days until 18 to 20 minims of solution 5 are given. That, in some cases is the highest protective dose. In the severest cases I find that the protective dose is about 15,000 pollen grain units. In this way through these various procedures I have been able to attain perfect results in 90 to 95 per cent of patients no matter how severe the previous pollen intoxications.

Discussion. The shortcomings of the 15 dose treatment sets on the market are as follows:

a. The protection dose is in none of the sets sufficiently high for a complete relief.

b. The series of injections should not stop at the dose which gives the reaction but should either repeat or go back to a weaker injection. In case of a constitutional reaction somewhere along the line the dose cannot be reduced or repeated on account of lack of material in the "treatment sets".

c. Instructions to the general practitioner by most pharmaceutical houses state that the last dose (15th) should be given at or about the beginning of the respective pollination periods. This conveys the impression to the physician and in turn to the patient that they are going to stay well and protected for the 6 to 8 weeks of the season, which is absolutely not justifiable. Only one out of 15 or 20 may remain protected. All others must have the maximum dose repeated every week for the season if protection is to be maintained.

d. The advice given by various clinics and certain manufacturers to increase the dose in the course of desensitization by 100 per cent or 50 per cent, is entirely wrong. A patient can never be favorably desensitized to a higher strength by consistent doubling of the strength of the injection.

In regard to reactions there are several considerations. The patient must be kept in the office for at least one-half hour following the injection so that in case of any reaction, from 3 to 5 minims of adrenalin may be administered.

After a reaction the following day's injection should be 2 minims below the dose which provoked the pre-

vious reaction. The dosage should gradually be worked up by 1 minim increases and after the previous reaction stage has been passed, increase may again be made by 2 minims.

Patients receiving dilution 5 should never be increased by more than 1 minim at a time. I have seen patients give violent reactions to, let us say, 7 minims of dilution 5. The following day they were given 5 minims of dilution 5, followed by a 1 minim increase every day, until receiving 10, 12, and even 15 minims without the slightest reaction. The presence of a reaction does not mean that the patient is protected. On the other hand, it merely reveals that the patient is not yet prepared for that particular dose and he must be worked up to it again by daily injections.

Occasionally one finds patients whom you cannot work up to the protection dose. Such patients occur in a proportion of 1 in about 15 or 20. In these cases increase of dose is halted and the highest dose the patient can receive without untoward reaction, is injected. In this type of patient we achieve 80 per cent favorable results, and even though the protective dose has not been reached, the symptoms, if any, will be mild. It has been my experience that such patients do reach their protective dose during the second year of treatment.

It is important to note that:

1. There are from 20 to 25 injections given before there is any possibility of reaching dilution 5.

2. The time interval is daily or even twice daily in the milder dilutions. All injections are to be given intradermally, if possible.

3. There are about 15 to 20 injections of dilution 5 necessary as a protective dose to be reached before the beginning of pollination of the summer (grass) and fall (weeds, etc.) seasons. For the spring (tree season) 12 to 15 minims of dilution 4 may be sufficient for the protection dose.

Patients receiving 15 to 20 minims of dilution 5 (equivalent to from 12,000 to 15,000 pollen grain units) are protected from any amount of pollen in the air; no matter how severely they have suffered in previous years, provided this dose is repeated once a week throughout the season.

It would therefore be necessary for the general practitioner in order to successfully treat a case of hay fever or hay fever and asthma, to buy in the open market 15 to 20 c.c. of a 3 per cent concentrated glycerol-saline pollen extract for the respective season which is indicated by preliminary testing, and to obtain from a local laboratory five or more vials of sterile 10 c.c. physiological salt solution which would enable him to make his own dilutions.

Continuation Treatment. I have used the "continuation treatment" for the past four years. This means to keep the patient under the maximum protective dose of pollen extract injected at the longest time interval throughout the year without inducing a reaction. It is practical and desirable in the class of patients who can stand the maximum protective dose repeated every three, four, or five weeks without a reaction. In about 5 to 10 per cent of patients the longest time interval, unfortunately, is not more than one week or ten days. Every time the maximum dose is injected every ten days or two

weeks the patients get a reaction The maximum dose has to be constantly reduced by 1 or 2 minims so that at the following season the patient should have daily injections for two or three weeks to work him up to the highest protective dose. Under these circumstances there is not much gained by the continuation method of treatment in this type of patient.

EXAMPLE OF PROCEDURE IN TREATMENT

Dilution 1A Each minim contains 28 Pollen Grain Units

2 minims
4
6
8
10
12

Dilution 1 Each minim contains about 57 Pollen Grain Units

4
6
8
10
12

Dilution 2 Each minim contains about 114 Pollen Grain Units

4
6
8
10
12

Dilution 3 Each minim contains about 228 Pollen Grain Units

4
6
8
10
12

Dilution 4 Each minim contains about 456 Pollen Grain Units

4
6
8
10
12

Dilution 5 Each minim contains about 912 Pollen Grain Units

4
5
6
7
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15

Cardiac Failure

Report of a Case of Cardiac Decompensation of Fourteen Months Duration

By Edward J. Stieglitz, M.S., M.D., F.A.C.P., *Chicago, Ill.*

IT is most unusual for cardiac decompensation with severe edema to persist for as long as fourteen months. Cardiac failure and its associated phenomena have been repeatedly described and discussed, but the present instance permitted of long and careful study throughout the latter course of the decompensation, and revealed a number of most significant phenomena which warrant discussion.

Report of Case

The patient, a widow with one child, was first seen June 25, 1928, at which time she was 55 years old. The chief complaint was marked dyspnea, occurring particularly upon exertion, but noticeable even at rest or when talking. Pedal edema was also noted. A similar period of breathlessness and edema had occurred in 1924. The past history revealed frequent attacks of tonsillitis as a girl and considerable intoxication during the one pregnancy in 1898. The climacteric had been very abrupt in 1923. Her habits were good with the exception of a rather too liberal use of condiments. Exercise had long been extremely limited, both because of the low threshold of dyspnea and because of her obesity (her weight ranged about 200 lbs., although the patient was but 4 ft. 11 in. in height). A lifelong history of migraine with typical cephalalgia and scotomata was elicited. The family history was significant in as much as both parents, one sister and two brothers had all died of cardiac failure, probably of the hypertensive type.

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Physical examination revealed a short obese elderly lady with moderately ashen subcyanotic facies. There were moist and crackling râles in the pulmonary bases. The left border of the area of cardiac dulness extended 12 cm. to the left; the right border was substernal. The second aortic sound was ringing in tone and accentuated; a very soft systolic aortic murmur was noted. The pulse was 98 at rest. The arterial tension was determined at 210/125 at rest, but fell to 180/120 upon minor exertion and to 152/100 upon the inhalation of amyl nitrite.[1] There was some pedal edema; dyspnea was marked upon very minor effort. The urine was normal.

The diagnostic summary made at this time noted the following:

1. Arterial hypertension with moderate arteriolar sclerosis.
   Probable etiologic factors:
   1. Hereditary influences.
   2. Obesity.
   3. Intoxication of pregnancy (1898).
   4. Frequent tonsillitis.
   5. Oral sepsis.
   6. Abuse of condiments.
2. Hypertensive heart disease;
   Early decompensation.
3. Obesity.
4. Former migraine.
5. Probable alveolar infection.

The patient was advised to rest, stop the use of condiments and meat extractives, have roentgenograms made of her teeth, take dried digitalis leaves, gr. iss, t. i. d., and bismuth subnitrate, gr. x, t.i.d.[3,4,5]

On July 2, 1928, the renal concentration test revealed a maximum specific gravity of 1.024, 30 mg. of albumin per hundred c.c., a few casts, no sugar. The dyspnea was much improved; the arterial tension was 200/90. On July 18 a large dental abscess was demonstrated. The dyspnea had disappeared and the arterial tension was 184/85. By August 18 the arterial tension had fallen to 178/82, the pulse to 80. When seen September 17 the patient had had a severe shock as a result of a holdup and burglary. Since then the dyspnea had returned; the arterial tension had risen to 220/104. With similar digitalis therapy and continuation of the bismuth subnitrate, on September 26 the pulse was 86, dyspnea almost gone and the arterial tension 180/88. It was noted in October that she felt much calmer and less unstable emotionally; the arterial tension was then 162/84, and in November, 172/93. The abscessed tooth had as yet not been attended to. The dosage of bismuth subnitrate was reduced to gr. x twice daily in October[6]. During 1929 the patient felt quite well, complained only of dyspnea and some precordial pain upon exertion; during this year the arterial tension was observed to be 165/85, 166/90, and 175/90. The immediate outlook for the patient was rather encouraging.

On January 17, 1930, the patient was seen at home. She had been acutely decompensated with very marked pedal edema, severe breathlessness even at rest, orthopnea and cough for 2 or 3 weeks. The cardiac failure had been induced by a coryza with cough. At this time the pulse was totally irregular with almost alternating extra systoles and ranging about 120 in rate. The arterial tension was 170/100. From then on for 14 months it was a continuous daily struggle with the decompensation with a multitude of therapeutic agents, some of known and others of undemonstrated value. Certain of the clinical phenomena such as variation in weight, pulse, arterial tension, nausea and dyspnea are best illustrated graphically (figure 2).

The termination of this extraordinarily prolonged congestive cardiac failure was unusual: a sudden occlusion of the left femoral artery caused gangrene of the left leg and such profound intoxication that the myocardium failed rapidly. Just prior to this fatal accident the patient was in better condition than at any time previously for a year. It is notable that throughout the prolonged decompensation with edema the urine was essentially normal. On March 9, 1931, the patient complained of sudden severe deep pain in both legs. This gradually became localized in the left leg and was not relieved by hot or cold packs or moderate sedatives. On March 10 it became necessary to administer 1/6th gr. of morphine sulphate; the left leg was hot, of a blotchy red, and very tender. A cellulitis in the edematous tissue was suspected. By evening the pulse had risen to 110, the temperature to 101.4° F. On March 11 the arterial tension had fallen to 125/70; the pulse was 120; temperature, 102°; the patient was semicomatose, very cyanotic and the leg revealed large blotchy areas of deep cyanosis extending up to a sharp border at mid-thigh. By evening of the next day these blotchy areas had formed huge watery blebs which drained bloody serum profusely. At 7:30 P.M. on March 12 the patient was in deep coma and extremely cyanotic; the pupils were large but rigid; respirations were 44 per minute; temperature, 102° F.; pulse, 110. At 9 P.M. the respirations were 48; pulse, 114; arterial tension, 112/40; at 11 P.M. respirations were 50 and more labored; pulse, 120; arterial tension, 104/35; at 12 midnight the tension had fallen to 98/32 and to 88/26 at 1 A.M. when the pulse was approximately 140 and totally irregular. The patient died at 1:42 A.M.

Necropsy. Only the essential observations will be recorded. The heart was very large and firm with most of the increase in size resulting from marked hypertrophy of the left ventricle. The right heart and the mitral valves were normal. The aortic valve was markedly stenotic and the cusps distorted. The valve ring was incompetent. Areas of calcification in the valve leaflets were quite extensive. The ascending portion and the arch of the aorta were smooth and glistening, without defects. Several coronary vessels upon being opened revealed

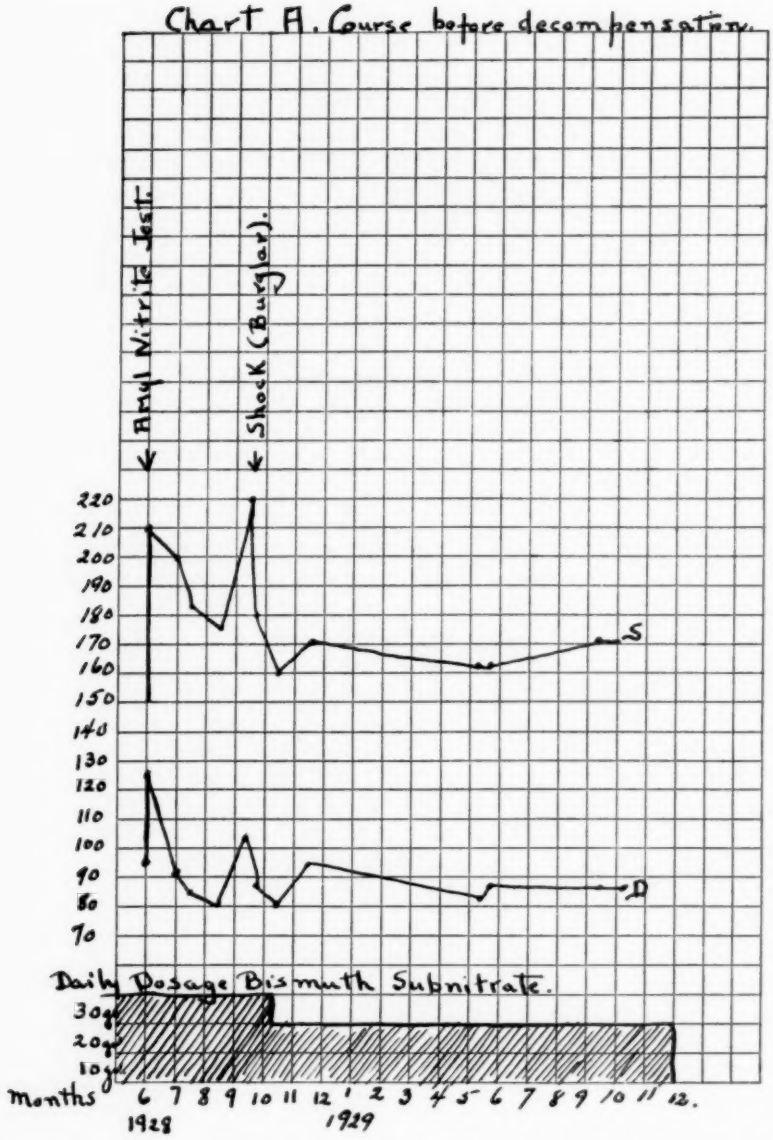

FIG. 1. Chart A. Course of the arterial tension under therapy with bismuth subnitrate prior to cardiac decompensation.

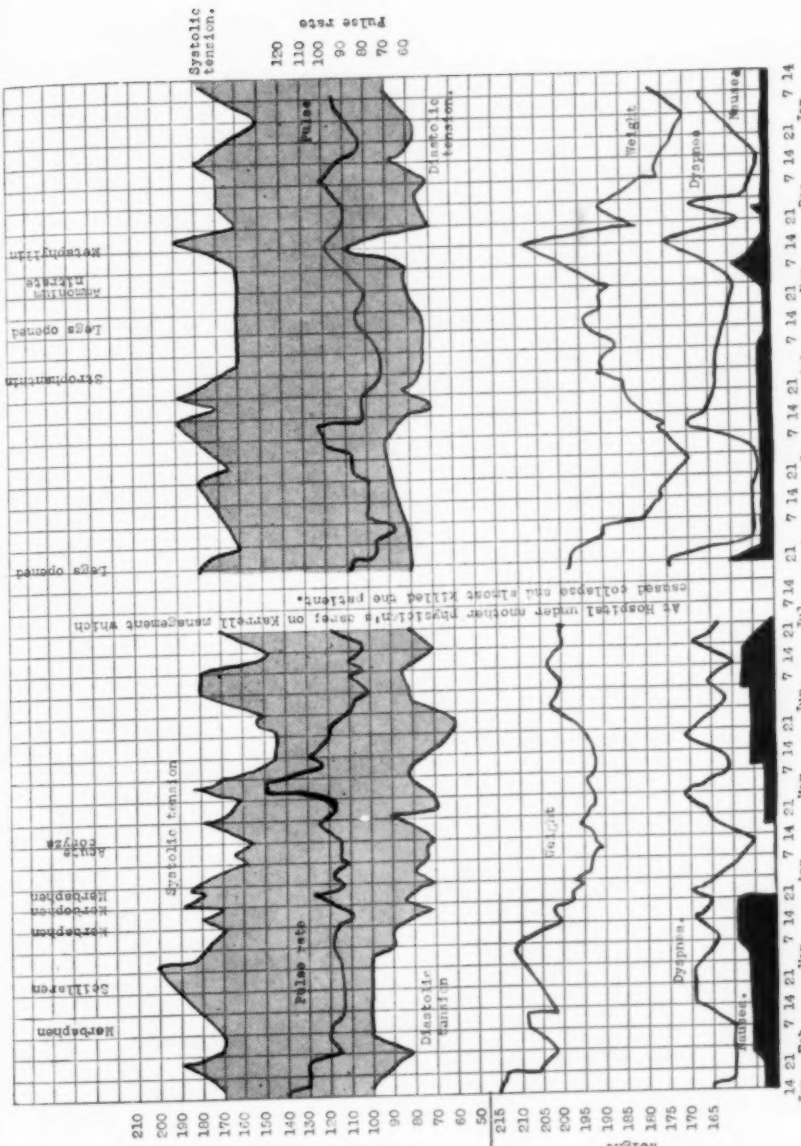

FIG. 2. Chart B. Record of clinical course from January, 1930, to January, 1931. The average arterial tension, pulse and weight are recorded. The pulse pressure is represented by the shaded portion of the chart between the systolic and diastolic tensions. The degrees of dyspnea and of nausea are indicated along the base of the chart. Medication is recorded very incompletely; throughout this period digitalis and appropriate sedatives were administered semi-continuously. During the first two weeks of July the patient was under another physician's care and on Karrell management. The course from January to March, 1931, is not included.

moderate sclerotic lesions. The pericardium was normal, as was the endocardium with the exception of the aortic valves.

The kidneys were of normal size, the capsules stripped readily and cut surfaces appeared normal. The liver was hard, pale, and large. Surfaces made by cutting appeared grayish, as though cooked. The spleen also was engorged, somewhat enlarged, and firm. In the left femoral artery a rather fresh thrombus occluded the lumen at about the upper third of the leg.

Microscopic Findings. Throughout the tissues studied, marked and extensive arteriolar changes were seen. In the kidneys, heart and spleen, these were most marked. There was extensive thickening of the media, hypertrophy of the spiral smooth muscle fibers and some fibrotic changes in the intima of the arterioles and pre-capillary arterioles. Some medial thickening of the vasa vasori of the aortic adventitia was noted.

The renal parenchymal structures were essentially normal; both the tubules and glomeruli failed to reveal any appreciable damage despite the very prolonged severe edema.

The hepatic cellular strands were widely separated by edema; intense fatty vacuolization of the hepatic cells existed, especially in the central portion of the lobules. Hepatic fatty degeneration is characteristic of prolonged anoxemia. The Kupffer cells were more prominent than is usual. The portal canals and biliary ducts were essentially normal.

The intimal and medial portions of the aortic wall were normal. Arteriolar sclerotic changes were noted in the vasa of the adventitia. The elastic tissue was not disturbed, nor was the tunica elastica intima abnormal.

The heart muscle stained very poorly with phosphotungstic acid. The fibers were some what shortened and thicker than usual. The normal striations, however, were not appreciably altered. The nuclei of the cardiac muscle were pale; a few pycnotic nuclei were noted. The usual spindle shaped accumulations of sarcoplasm about the nuclei were not demonstrated. No evidences of focal or inflammatory lesions were found. Both the smallest and larger coronary arteries seen on section revealed markedly thickened and hypertrophied medial layers—the medial muscular hypertrophy of hypertensive disease.

The aortic valve revealed extensive heavy calcification, chiefly at the base of the valve. The endothelium of the valve margin and sides was normally intact. Calcification, partially stratified, appeared along the valvular attachment; being densest along the center of the valve leaflet and in two bands below the subendothelial reticulum. A vas vasori sectioned at the valve base revealed marked sclerotic narrowing with intimal proliferation. Such findings are in agreement with previous observations[7] which indicate that such aortic valve calcification may be largely due to ischemia induced by impaired vascular supply.

Comment

The above brief resumé of the course of this unusually prolonged instance of cardiac failure merely outlines the sequence of events and does not touch upon the profound significance of a number of phenomena and the related therapeutic problems.

The comparative value of various therapeutic agents was demonstrable because of the opportunity for prolonged observation. Certain aspects of the complex problem of edema of circulatory origin are worthy of emphasis. The behavior of the arterial tension, and particularly the pulse pressure, deserves consideration. The most unusual termination by thrombosis of a peripheral artery in an edematous extremity warrants recording.

At the very onset of the cardiac decompensation it was made clear that medication intended to reach and to affect the heart had to be administered in such a manner that delivery to the site of action was assured; medication was by intravenous injection. Digitalis

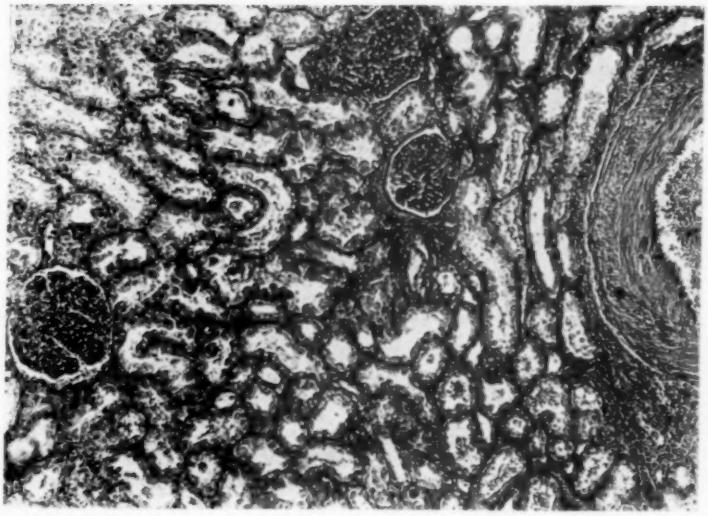

FIG. 3. Kidney, magnified 77.5 diameters; hematoxylin and eosin stain. The tubular and glomerular structures are essentially normal. The medium sized artery shown on the right reveals extensive thickening of the media and some intimal proliferation.

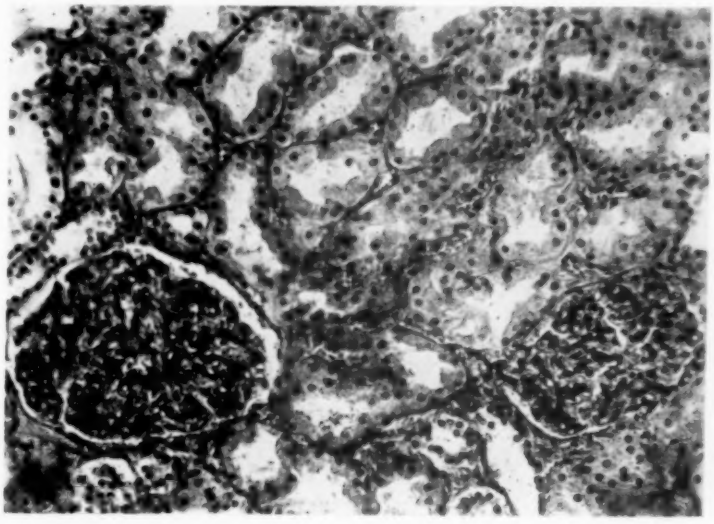

FIG. 4. Kidney, magnified 154 diameters; hematoxylin and eosin stain. The normal appearance of the tubules and glomeruli are well demonstrated here; there is some edema of the stroma.

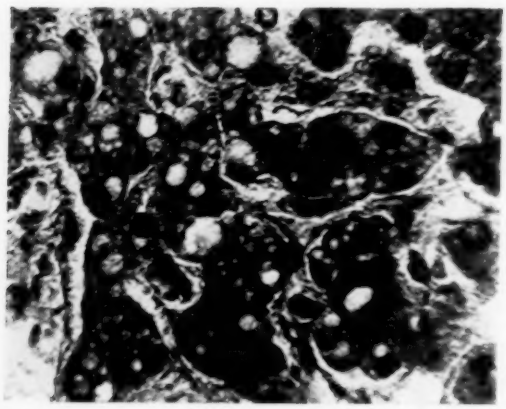

FIG. 5. Liver, magnified 232.5 diameters; phosphotungstic acid, hematoxylin stain. Fatty degeneration of the parenchymal hepatic cells. Increase in size and depth of stain of the Kupffer cells of the sinusoids, notable in the center of the field.

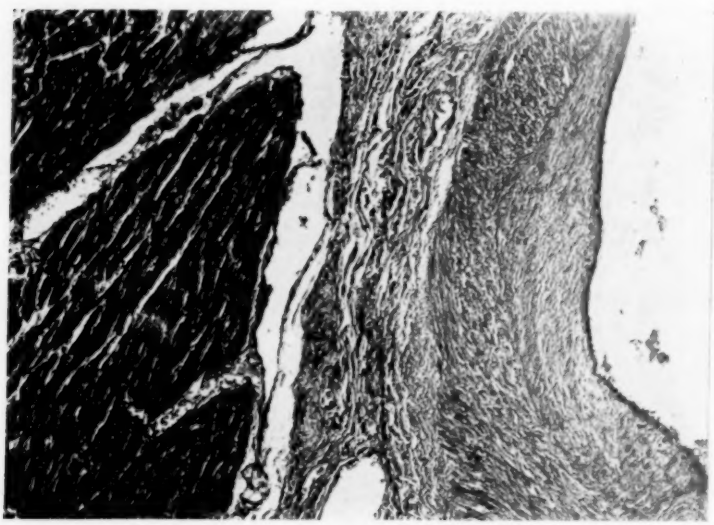

FIG. 6. The myocardium, pericardium and part of a coronary artery, magnified 77.5 diameters; hematoxylin and eosin stain. Thickening of the medial and intimal coats of the arterial wall notable.

administered by mouth failed to have any effect upon the pulse rate early in the course of decompensation when there was extensive intra-abdominal edema and ascites and when the edema was increasing. It must be realized that in the presence of extensive edema the alimentary absorption of digitalis, or any other drug is greatly interfered with.[3, p. 182] The gastro-intestinal tract is edematous, as are the other tissues, and apparently most of the drug is retained in the edematous tissue[8,9]. Subcutaneous administration into edematous tissue is similarly inadequate[10,11]. It is necessary that digitalis, and similar acting principles actually be delivered to the heart,[12] the site of action. Digitalis, although strengthening the force of cardiac systole, does not cause a rise in arterial tension.[13] The diastolic pressure is usually lowered by the improved efficiency of the circulation, which produces increased renal secretory efficiency and greater elimination of toxic waste. Improvement in the circulatory efficiency likewise results in more effective cerebral circulation. As the prime purpose of digitalis medication is to slow the pulse,[14] it should be administered in adequate dosage. The danger of cumulative effects of digitalis has been exaggerated.[15] Most patients suffer far more from inadequate than from excessive administration.[16,17]

Toxic effects of overdosage of digitalis are usually first manifest as nausea and vomiting; later diarrhea, cephalalgia and disturbances of vision[28] may appear, with heart block occurring in instances of marked overdosage.[18] The nausea, vomiting and diarrhea have been attributed to reflex action from the heart, not to direct gastro-intestinal irritation.[19,20,21] The secondary toxic effects of squill or strophanthin are similar. In the present instance of cardiac decompensation it was repeatedly observed that preparations of squill ("Scillaren," Sandoz) created more nausea than did digitalis. Strophanthin, likewise produced more nausea than digitalis. For many months the patient either was distressingly dyspneic because of relatively inadequate digitalization or she was emphatically nauseated. Neither squill nor strophanthin preparations revealed any clinical advantages over digitalis throughout the course of the decompensation.

Because of the marked disadvantage of nausea induced by adequate digitalization, during the last several months of the cardiac decompensation, coramine, a relatively new synthetic cardiac and respiratory stimulant, was given a trial. It was found to be equal to digitalis in effectiveness in maintaining a slower pulse and caused no nausea or gastro-intestinal distress.[22] Coramine was well tolerated and was efficient in controlling the severe and distressing dyspnea and orthopnea.[23] Coramine is synthetically produced; its chemical composition is pyridine-beta-carbonic acid-diethylamide.[24] There was no evidence of cumulative effect, nor was there any indication that tolerance to the drug was being acquired.[25] Coramine is said not to depress the auriculo-ventricular conductivity as does digitalis.[26]

Not only is it subjectively distressing for the patient to be semi-continuously nauseated, but it is objectively most undesirable because nausea so

greatly interferes with proper nutrition and caloric maintenance. This was repeatedly demonstrated in the present instance: whenever nausea and anorexia prevented the patient from taking an adequate diet, the cardiac insufficiency was augmented. It has been emphasized by Smith, Gibson and Ross[27] that an adequate glucose intake is essential for recuperation of injured myocardial tissue. For this reason alone it is most important not to aggravate the anorexia of the very sick patient. As it is most illogical to anticipate active reparative rehabilitation of injured tissues under conditions of tissue undernutrition or inadequate oxygen supply, maintenance of an adequate hemoglobin content of the blood is of similar significance.

The behavior of the pulse pressure during this prolonged period of cardiac inadequacy was most instructive. It was noted (see figure 2) that whenever the cardiac efficiency declined there occurred a marked depression of the diastolic tension with a corresponding increase in the pulse pressure. These changes occurred frequently whenever exertion, excitement, transient coryza or excessive fatigue further exhausted the myocardium as evidenced by greater rapidity of the pulse rate, greater dyspnea and gains in weight due to increasing of the edema. It has long been taught[29] and correctly, that diminution of the myocardial efficiency results in reduction of the systolic tension and pulse pressure and that such reduction is of ominous prognostic import.[3] The pulse pressure may be considered a rough measure of the stroke volume,[30] which is ordinarily reduced in cardiac exhaustion. The pulse pressure usually falls in myocardial exhaustion with tachycardia but is increased in thyrotoxic tachycardia[31] in proportion to the elevation of the basal metabolic rate, and the increased cardiac volume output. However when the aortic valve is incompetent, the diastolic tension is lowered and the pulse pressure markedly increased. In this patient aggravation of the cardiac inadequacy led to further left ventricular dilation and dilation of the aortic ring. The fact that the aortic valve was calcified was unknown at the time these observations were made. As pointed out by Christian[32] calcification of the aortic valves is most frequently undetected clinically when hypertension co-exists. Such aortic valvular calcification is more frequent in males, is very slowly progressive and usually asymptomatic until cardiac decompensation occurs; excessive left ventricular enlargement is the rule as in the present instance. Of 22 cases mentioned by Christian, in 19 the Wassermann was negative; rheumatic infection early in life, as in the present case, is the predominant etiology. Characteristic of such lesions is the asymptomatic course prior to the final and usually brief decompensation.[32]

Although diminution in pulse pressure is the usual rule during cardiac decompensation and should serve as a warning of impending disaster[3] the reverse may occur because of dilation of the aortic ring and the creation of a state of aortic incompetence. The unwary may be led astray if this is not kept in mind. The presence of murmurs in the aortic area assist but do not make sharply definite a diagnosis

of aortic regurgitation induced by dilation: during cardiac decompensation irregular murmurs all over the precordium both systolic and diastolic in time, obscure their significance. Reduction in diastolic tension *under these conditions* was of ominous prognostic import although the more usual phenomenon is diminution of the systolic arterial tension without great change in the diastolic tension.

Evaluation of the prognosis in the present instance was based upon a number of important considerations; no one factor may be utilized as the sole criterion for prognostication.[1] Of importance are the following factors: (1) history of previous decompensations; (2) the etiologic background of prolonged extensive hypertensive disease; (3) the evidence of aortic insufficiency; (4) the age of the patient; (5) the marked obesity for many years; and (6) the failure of the heart to respond adequately to energetic digitalization. Repeated attacks of cardiac failure reduce the cardiac reserve with each decompensation; some of the surplus or reserve is destroyed with each struggle for returned compensation and a smaller and smaller margin of safety remains. As many as eight instances of cardiac decompensation in the same patient have been observed.[3]

The etiologic background of prolonged and extensive hypertensive disease affected the prognosis adversely. It may be stated as a dictum of clinical experience that in prolonged hypertensive arterial disease myocardial injury exists *a priori*.[3, p. 157] The myocardium is embryonically, anatomically and functionally a specialized portion of the arterial media, (the site of injury and change in hypertensive disease) and is therefore open to the same sources of injury as initiate the original vascular disease. In addition to this myocardial injury is the factor of fatigue, engendered through excessive and unremitting work in overcoming the high peripheral resistance. Myocardial nutrition is impaired by the malcirculation resultant from coronary arterial disease; such ischemic asphyxial intoxication is a most significant factor. The paroxysms of precordial pain in angina pectoris are apparently the result of cardiac anoxemia.[33] This anoxemia is enhanced by anemia. In the present instance, therefore, it was amply justifiable to assume extensive myocardial injury independent of the valvular disease and myocarditis possibly initiated by the frequent attacks of tonsillitis during the patient's later childhood. The presence of the aortic diastolic murmur, evidencing an aortic regurgitation, further darkened the prognosis. The age of the patient precluded any of the phenomenal recuperative powers of youth and the obesity placed a greatly increased burden upon the faltering myocardium which failed to respond to the intensive digitalization promptly induced at the beginning of the present decompensation. It was primarily in this respect that this third and last attack of cardiac decompensation differed at the onset from the second attack observed 18 months previously. This failure to respond could only indicate one thing: that the myocardium was now most thoroughly exhausted and had almost no reserve to fall back upon.

Aside from the distressing dyspnea

and orthopnea the severe edema or anasarca was the most distressing clinical phenomenon. Throughout the course of the terminal illness the edema was profound; most of the time the patient retained from sixty to eighty pounds of edema fluid. A number of most significant considerations in this condition warrant discussion.

Edema may be defined as any undue accumulation of fluid in the tissues and tissue interstices. For many years it was thought that such accumulation was due to the failure of the kidneys to adequately secrete water. This is not the case, however. The oliguria results from the failure of the renal tissues to receive free water for secretion as urine, the water being held by the tissues. The correction of the earlier erroneous conception, has been due largely to the significant researches of J. Loeb,[34] Fischer,[35] L. Loeb,[36] Aldrich and McClure,[8,10] Andrews[37] and many others. To attempt any comprehensive discussion of edema here is impossible. For our clinical purposes, however, a number of salient conceptions need emphasis. The mechanism of the production of cardiac edema is probably very similar to that of toxic or so-called renal edema; in both instances edema being due to tissue intoxication, alteration of the hydration capacity of the tissue colloids and increased avidity of the tissues for the accumulation and retention of water. Whether these changes be due to circulatory inadequacy as in congestive heart failure, or to intoxication in renal disease is relatively immaterial for our present purpose.

Edema has come to be considered a protective mechanism; possibly an attempt on the part of the tissues to dilute and retain toxic noxa in relatively unimportant structures and thus spare the vital parenchymatous organs. It is notable that the earliest and greatest accumulations of edema fluid are in the skin, extremities and serous cavities, whereas absolutely essential structures such as the heart, kidneys, brain and liver are involved to but a minor degree. In part this may be due to the much greater expansibility of these sites of predilection, in part it may be considered teleologic evidence of the conception that edema is a protective mechanism. Nephritic children become profoundly intoxicated and may develop uremic convulsions if edema is rigidly repressed by deprivation of adequate fluid intake. Convincing evidence makes necessary a change in our original definition of edema in the clinical sense: edema is any undue accumulation of fluid in the tissues or tissue interstices due to changes in the tissues, causing retention of fluid by them and *associated with the accumulation of toxic matter*. Edema fluid is toxic.[37] The toxicity of the edema fluid was repeatedly and conspicuously demonstrated in the present instance of congestive heart failure. It is inconceivable that such extensive accumulations of fluid should persist for many months without being laden with toxic metabolic products.

Whenever diuresis was successfully, although temporarily, induced by any method the patient promptly became profoundly intoxicated: the pulse rate rose, dyspnea increased, anorexia, nausea and vomiting became more pronounced, cyanosis deepened and the patient felt intoxicated as though by an

infective process. The more rapidly the edema fluid was shifted from the tissues into the circulation the more marked was the intoxication. This was strikingly manifest during an attempt at edema reduction by Karrell management[38] with severe restriction of fluid intake (200 c.c. milk four times a day and nothing else), undertaken by another physician. This procedure almost killed the patient; the severe restriction of fluids led to such a profound intoxication that the patient became comatose. Only through the prompt introduction of fluids was disaster prevented at that time.

Thus the problem of the treatment of edema is not merely the problem of removing the water of the edema fluid, but consideration of the removal of the very toxic solutes is essential. That these toxic solutes are a real menace is incontestable. Mere transfer of the toxic fluid from the tissue spaces into the circulation is most detrimental; this places the noxa where great damage can be done to the essential parenchymatous structures. On one occasion, Nov. 13, 1930, in the present instance, the patient lost 19 lbs. in 16 hours by diuresis induced by intravenous metaphyllin: this rapid liberation of fluid so profoundly intoxicated the patient that she became semi-comatose and the arterial tension rose to 240/130, causing a transient hemiplegia and aphasia which persisted for 36 to 48 hours.

Such intoxication represents a detriment which far outweighs the benefit of weight reduction through the loss of fluid. It appears immaterial by what medication diuresis is induced; theobromine, theocalcin, metaphyllin, euphyllin, potassium salts, calcium gluconate,[43] calcium chloride and ammonium nitrate[39,40] were all used in connection with digitalis, scillaren or strophanthin. Small doses of dessicated thyroid[41] with coramine (no nausea) produced a more persistent and less intoxicating diuresis. Hydrogogue catharsis, as with elaterin, caused marked exhaustion and debility; the loss of fluid was but temporary.

It is of essential importance in the treatment of edema that everything possible be done to assist in cardiac repair and rehabilitation for the primary factor in the causation of such edema is the circulatory failure. Retardation of the exhausting rapid pulse by digitalis or related drugs is of the greatest importance. Adequate nutrition, especially with carbohydrates, is necessary. Oxygen debt may be reduced by the use of an oxygen tent; the diminution in cyanosis and anoxemia is often remarkable.[44] It is in the advent of these direct cardiac measures being inadequate in reduction of the edema that the other methods of attack must be utilized.

Removal of edema fluid by mechanical means permits of partial relief of the anasarca without liberation of the very toxic debris into the circulation. Should extensive accumulation of fluid occur in the serous cavities, this is readily accomplished by paracentesis or repeated thoracentesis. In the present instance, however, the edema was dependent; the patient's legs were huge and of almost boardlike hardness up to the mid-thigh. It was only occasionally that evidence of intra-abdominal accumulation of fluid could be elicited; the thorax and upper extremities were at no time edematous. On

two occasions incisions were made in the legs, on either side of the edematous ankles, with most gratifying drainage after the first procedure. After these incisions (about 10 c.m. long and 3 c.m. deep into the subcutaneous tissue) had been made, the weight of the patient fell from 202 lbs. to 172 lbs. in three weeks, losing 20 lbs. in the first five days. This was the only occasion when such marked weight loss (edema loss) was not accompanied by the severest form of intoxication. During and following this period the patient felt unusually well and energetically strong.[42] Gradually, however, because of the persistence of the circulatory inadequacy, the extremities became more and more edematous again and a second attempt on Oct. 14, 1930, to produce free drainage resulted in a temporary loss of approximately 10 lbs. in 10 days. On this second occasion drainage was scant and slow; the edema had become more firmly "fixed" in the intoxicated tissues and was retained with great tenacity: the tissue thirst[3,8,9,10] had become more marked. Such surgical intervention in extensive edema of the extremities, of course, does not alter the hydration capacity of the tissue colloids so as to cause them to give up their bound water, nor does it in any way effect the etiologically significant malcirculation, except inasmuch as there is reduction of the mechanical obstruction due to the edema. Therefore the limitations of such mechanical drainage are notable; no physiologic diuretic effect is to be anticipated. However, the administration of the xanthin diuretics greatly increases the flow of serum from the wounds and it is felt that this is most desirable. The one great advantage of such a route of elimination for the edema fluid is that the toxic debris and "edema toxins" are *not thrown into the circulation;* diuretic medication to the tissues liberates more of the fluid and thus the flow is enhanced.

Three important and often neglected clinical aspects of the problem of circulatory edema were repeatedly emphasized during this long struggle: edema fluid is poisonous; edema fluid caused profound intoxication when thrown rapidly into the circulation; concentration of these toxins by water deprivation increases the intoxication to a dangerous degree and for this reason the patient should be protected by an adequate fluid intake during diuresis and the subsidence of edema. Water itself is probably the safest diuretic if used with judgement and discretion. If edema is considered a protective mechanism, which we believe to be the case, the objective of therapy should not be limited to removal of the water alone but should consider of primary importance the removal, or the rendering innocuous, of the very toxic solutes in such fluid. Very rapid diuresis is dangerous, particularly in instances of edema of long duration. Dilution of the fluid by liberal water intake is desirable.

It is most important to realize that both clinically and pathologically there was no evidence of notable renal disease in the present case. Frequent analyses of the urine revealed a few casts, some epithelial débris, from 10 to 30 mg. albumin per hundred c.c. (sulphosalicylic acid method), no sugar or pus. Anatomically at autopsy the renal tissue showed little or no parenchymatous

change both grossly and microscopically. The pathologic picture was that of long standing hypertensive arterial disease with arteriolar sclerosis,[3] but no nephritis. Secondary injury, attributable to the hypertensive disease, was primarily cardiac. The unusual terminal accident of thrombosis of the femoral artery deserves a word of comment. What is most extraordinary is that arterial occlusion in an edematous extremity does not occur more often. So far as our search has gone we have been unable to find any other reported instances of such termination in congestive cardiac failure. The origin of the thrombosis was undoubtedly embolic, probably from the diseased aortic valve leaflets. It is but a very remote possibility that the surgical wounds about the ankle had anything to do with the arterial occlusion: they were clean and free from infection throughout the course and the occlusion occurred from above, not below. Occlusion of the femoral artery does not necessarily result in gangrene of the extremity as normally the collateral circulation suffices to maintain adequate nutrition; in the present instance, however, the severe and prolonged edema markedly impeded the circulation and did not permit of sufficient oxygenation. Although the original prognosis had never been good, such an accident must inevitably mark the beginning of the end.

Summary

In an unusually prolonged instance of congestive cardiac failure with extensive edema a number of pertinent clinical phenomena have been studied and reported. Clinical evaluation of a number of therapeutic agents is made. The behavior of the arterial tension during decompensation is discussed and the bases for the evaluation of the prognosis considered. Certain significant aspects of the clinical problem of edema in cardiac decompensation are emphasized. Another instance of aortic stenosis with calcification of the aortic cusps, recently described by Margolis and his associates[7] and Christian[32] as a distinct clinical entity, is recorded. Report is made of the unusual feature of termination by occlusion of the femoral artery in an edematous extremity.

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Two Ways of Dealing with Unqualified Medical Sectarians

"THERE are two ways of dealing with the problem constituted by the existence of unqualified medical sectarians. One is the non-legal, and involves striking at the cultists by removing the causes which lead people to go to them. The second involves the legal suppression of the sectarians. The first approach, being the more fundamental, is in the long run the simpler and more effective. The major factors responsible for the growth of cults are credulity, ignorance, and superstition on the part of the public. It is obvious that if the cults are to be eradicated, these failings must be remedied and people must learn more about the make-up and functioning of the human body. Furthermore, it is only as people gain an intelligent understanding of the human body that they can be led to understand the necessity for legal suppression of unqualified healing practitioners. To the extent that certain deficiencies in medical practice have contributed to the rise of present-day sects, the removal of those deficiencies will aid in the eradication of the sects.

"The second way of eliminating unqualified sectarians is through laws regulating the healing art. At the present time in the United States the legislative regulation of the healing art—regulation designed to protect the public from unqualified practitioners—is not accomplishing its acknowledged purpose. All it does is to maintain high standards for one group of practitioners. Quite illogically, it also sanctions the existence, on a lower plane of qualifications, of many thousands of poorly trained practitioners. Manifestly, if the public is to be adequately protected, there must be a single minimum standard of qualifications for all healing practitioners."

From *The Healing Cults—A Study of Sectarian Medical Practice: Its Extent, Causes and Control.* By LOUIS S. REED, Ph.D. The Committee on the Costs of Medical Care, 910 Seventeenth Street, N.W., Washington, D.C. (Abstract of Publication No. 16.)

Generalized Myositis Fibrosa

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LOCALIZED disease of the muscular system of an acute or subacute nature, commonly designated muscular rheumatism, fibrositis, myositis, or myalgia, is of very common occurrence. Pemberton[1] has remarked that it is probably one of the most widespread and frequently occurring conditions to which human beings are subject, excepting mild infections of the upper respiratory tract. Quite in contrast to the above statement is the fact that inflammatory muscular diseases of a generalized nature, either acute, subacute, or chronic, are exceedingly rare. In the acute and subacute group four types are recognized: primary suppurative myositis which is only occasionally generalized; myositis, a result of *Trichinella spiralis* infestation; dermatomyositis; and polymyositis hemorrhagica, which is probably a form of the latter condition. In the chronic group there are three types: the chronic form of dermatomyositis; myositis ossificans progressiva; and primary myositis fibrosa. The latter condition, primary myositis fibrosa, is presumably the rarest of all types, there being only four typical cases reported in the literature, with perhaps as many doubtful or atypical ones.

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Résumé of the Literature

Janicke[2] in 1895 reported the first typical, authentic case of generalized myositis fibrosa. Prior to this time Gies[3] (1879) and Kreiss[4] (1886) each described a case of myositis fibrosa which, however, can hardly be regarded as typical since the extent of the involvement of the muscles was small, the lower limbs only being affected, but particularly because there was also involvement of the overlying skin. Gowers[5] (1899) in a lecture on polymyositis described an unusual case which has been designated as a case of myositis fibrosa in a recent review of the literature.[6] In this case the intense pain at the onset of the illness, the early appearance of foot drop, and the loss of deep reflexes leads us to believe that the condition was perhaps a peripheral neuritis of widespread distribution with secondary atrophic changes in the muscles. Moreover, histological evidence to support the diagnosis of myositis fibrosa is lacking. The case of Batten[7] (1904) was the first to be accompanied by a

detailed pathological study. In 1923 Burton, Cowan, and Miller[6] reviewed the literature and contributed an additional case. Hoover[8] (1924) has briefly described a case which appears to be quite typical; however, it was not proved by histological examination of tissue. The same author reported a case of dermatomyositis (case 3) which is somewhat atypical for that disease in that the characteristic skin changes were not present and which, to the present writers, seems to resemble myositis fibrosa. Rosenstirn[9] in his extensive review of the published cases of myositis ossificans progressiva found two cases which he thought had been erroneously diagnosed and which had extensive fibrous changes in the muscles rather than ossification. The first of these (Lexer,[10] 1895) was characterized by a generalized distribution throughout the muscular system of fibrous nodules containing calcareous material. The second case is that reported by Krause and Trappe[11] (1907), and was thought by Rosenstirn to be a case of myositis fibrosa. In this case, the multiple nodules, many of which had undergone softening, and the extensive changes present in the skin would cast considerable doubt as to the validity of Rosenstirn's correction. Perhaps the most that can be said of both cases is that if they belong to this group they are exceedingly atypical.

Etiology

Little if anything is known concerning the etiology of this rare disease. It seems rather likely that it is related pathogenetically to the localized myositides in that the histological picture of the muscle tissue in generalized myositis fibrosa does not differ greatly from that in the later stages of fibrositis. If so, the disease may be added to that already very large group designated as the rheumatoid or arthritic syndrome. Batten[7] suggested the possibility of this condition being allied to myositis ossificans progressiva largely because his case exhibited microdactylia of the large toes. Several facts concerning the two diseases renders this relationship not impossible. Ossification of muscle tissue in nearly all cases is preceded by a myositis. According to Rosenstirn,[9] the primary pathological change in myositis ossificans is capillary hemorrhage, and Llewellyn and Jones[12] have shown that the early change in fibrositis is a dilation of the small blood vessels and capillaries, with not infrequently minute hemorrhages.

Case Report

O. E., a negro boy, 14 years of age, a student by occupation, entered the John Sealy Hospital, January 3, 1929, complaining of stiffness of the entire body and pain in the chest.

Family History. Mother and father living and well, age 51 and 57, respectively. Five brothers and six sisters all living and well, the oldest being 33, the youngest 10 years of age. Negative history for syphilis, tuberculosis, and cancer.

Past History. Born at full term, normal delivery, the eighth child. He began walking at the age of 2. He was somewhat slow in talking and always stuttered badly. At the age of 7 he started to school and seemed to make normal progress, attaining the fifth grade at the onset of his illness. During childhood he was unusually healthy and the only disease which he had had was measles at the age of 9, from which he made an uneventful recovery. At the age of 10 he helped on the farm picking and chopping cotton. He was regarded by his family as being a perfectly normal child, except for

the stuttering, until the beginning of the present illness.

Present Illness. About one year prior to entry into the hospital he noticed a dull aching pain in the upper part of the chest. This symptom was present more or less continuously and was not intensified by respiration. He consulted a physician who gave him some medicine which caused the pain to disappear. At about the same time his mother noticed that he was not as "pert" as usual and that he seemed to move rather slowly and deliberately. However, he continued to go to school and to do odd jobs around the house. A few weeks later he noticed a peculiar stiffness in his hands which made it difficult for him to perform the finer movements without clumsiness. This stiffness slowly but progressively became worse. Four or five weeks after the recognition of the stiffness of the hands he noticed a similar state of affairs beginning in his legs which seemed to largely involve the knees and which interfered to some extent with walking. In September, seven months after the onset of his illness, he started to school as usual, but was unable to play with the other children as he had previously done because of clumsiness in walking and running. While doing calisthenics he noticed that he was not able to bend over as far as the other children and that his back seemed to be stiff and rigid. His appetite had remained good throughout his illness and as far as he could tell he had lost no weight. There was no constipation, nocturia, or polyuria. At no time during his illness had there been any fever or pain in his muscles or joints.

Physical Examination. The general appearance was that of a dull, apathetic negro boy of about 15 years of age. He stuttered badly when he attempted to speak. Height, 5 feet and 9 inches, weight 117 pounds; calculated ideal weight, 140 pounds.

The facies were non-expressive. No cervical adenopathy was present. The skin immediately surrounding the mouth was lighter in color than that of the face but no induration was present. The conjunctivæ and mucous membranes of the mouth were paler than normal. The teeth were in good condition. The tonsils were present, moderate in size and innocent in appearance.

The chest was of the asthenic type. Some deepening of the supra- and infra-clavicular fossae was noted. There was very little movement of the chest wall during respiration, breathing being entirely abdominal in character. Palpation and percussion resulted in negative findings. On auscultation the breath sounds were puerile, no râles were heard and the transmission of the spoken voice was normal throughout.

The cardiac impulse was diffuse in the third, fourth and fifth interspaces to the left of the sternum. No enlargement was made out by percussion. The heart sounds were loud and distinct. No murmurs were heard. The pulmonic second sound was markedly accentuated. The pulse rate was 88 and regular; the blood pressure, 116 mm. Hg. systolic, and 70 mm Hg. diastolic. There was no evidence of arteriosclerosis in the peripheral vessels.

The abdomen was scaphoid. The liver and spleen were not palpable and there were no masses or areas of tenderness. Rectal examination was negative. The genitals were normally developed. Both testicles were present in the scrotum. The prostate was normal in size, shape, and consistency.

The skin over the entire body was apparently normal except over the wrists and hands, where it was shiny in appearance and seemed somewhat thinner than normal. However, it was pliable and not bound down to the underlying tissues. The hair was normally distributed over the body.

Practically all the muscles of the body, but some more than others, seemed to be indurated. To the palpating hand they imparted the sensation of being firmer and stiffer than normal, and not unlike a sandbag. The muscle volume was fairly well preserved, with the exception of the deltoid and pectoral muscles which showed considerable atrophy. None of the muscles were painful either on palpation or movement. They seemed to have lost much of their normal elasticity with resulting limitation of movement. All movements of the face and lips were well performed. The masseter muscles were involved to such an extent that when the mouth was opened as

widely as possible the distance between the incisor teeth was only 3 cm. The sternomastoid muscles were only slightly involved. The arms could be abducted only to an angle of about 60° with the chest wall and at that point further abduction was prevented by tightening of the tendons of the pectoral and latissimus dorsi muscles (figure 1a). Extension of the elbows was possible only to an angle of about 160° because of shortening of the biceps muscle (figure 1b). Flexion of the elbows was not interfered with. Passive movements of the wrists were easily performed within a certain range but were abruptly checked by a tightening of the flexor and extensor tendons. The fingers were held in a semiflexed position and any attempt to extend them fully was thwarted almost immediately by tightening of the flexor tendons. The muscles of the trunk and lower extremities were uniformly involved. The knees could be flexed only to an angle of approximately 100° due to shortening of the quadriceps femoris muscle (figure 1c). The strength of all involved muscles was definitely impaired. There was a very feeble grip of either hand.

The gait was somewhat spastic. All the cranial nerves were normal. Fundus examination was negative. All deep and superficial reflexes were present and equal. There was no disturbance of sensation anywhere in the body nor was there any paralysis.

Laboratory Examinations. The urine was entirely negative. There was a slight secondary anemia present: hemoglobin, 75 per cent (Sahli); red blood cells, 4,050,000 per cu. mm.; white blood cells, 12,000 per cu. mm., with essentially a normal differential count. The blood and spinal fluid Wassermann tests were negative. Blood chemistry: total non-protein nitrogen, 30 mg.; urea nitrogen, 11 mg.; uric acid, 5.7 mg.; creatinine, 1.3 mg., and sugar (fasting) 91 mg., per 100 c.c. of blood. Spinal fluid examination was entirely negative. The basal metabolic rate was plus 14. The phenolsulphonphthalein excretion was 55 per cent in two hours. An electrocardiogram showed sinus rhythm with low voltage in all leads with slurring of the Q-R-S complexes. All T waves were upright. X-ray examination of the teeth, wrists, joints of the fingers, elbows, sella turcica, and skull were entirely negative.

Course in the Hospital. On admission the patient was afebrile but a week later he began to show a slight afternoon rise in temperature, 99° to 99.6° F. The pyrexia continued and gradually increased in degree. Two weeks later he complained of attacks of dyspnea which were especially troublesome at night and which were often accompanied by a dull aching pain over the precordium. He began to lose weight, 2 to 3 pounds a week. On several examinations of the chest it was now noted that moist râles were present in both apices. After a stay in the hospital of about two months the elevation in temperature became a more or less constant feature, usually reaching 101° F., in the afternoon. A tachycardia was constantly present. The physical signs in the chest became more pronounced and an X-ray study revealed evidence of an infiltrative lesion in both apices, which was thought to be tuberculous in nature. There was no cough or expectoration and as a result sputum could not be obtained for examination. Weakness became a prominent symptom and eventually he was confined to bed. Dyspnea was evoked on the slightest exertion. His condition gradually became worse and death occurred three months after admission.

Autopsy. Necropsy was performed five hours after death. Rigor mortis was present. On incising the pectoral and abdominal muscles they appeared to be lighter in color than normal and to cut with increasing resistance. The heart weighed 280 gm. The valves were normal with the exception of the pulmonic leaflets which showed slight fenestration. The myocardium was abnormally light in color. The left lung contained an area of consolidation in the lower portion of the upper lobe and the overlying pleura was dotted with greyish nodules measuring 1 to 2 mm. in diameter. Section of this region of the lung revealed multiple areas of caseation. The right lung was apparently normal. The hilus nodes were enlarged and on section showed multiple greyish areas. The mediastinal nodes were likewise enlarged and on section were grey-

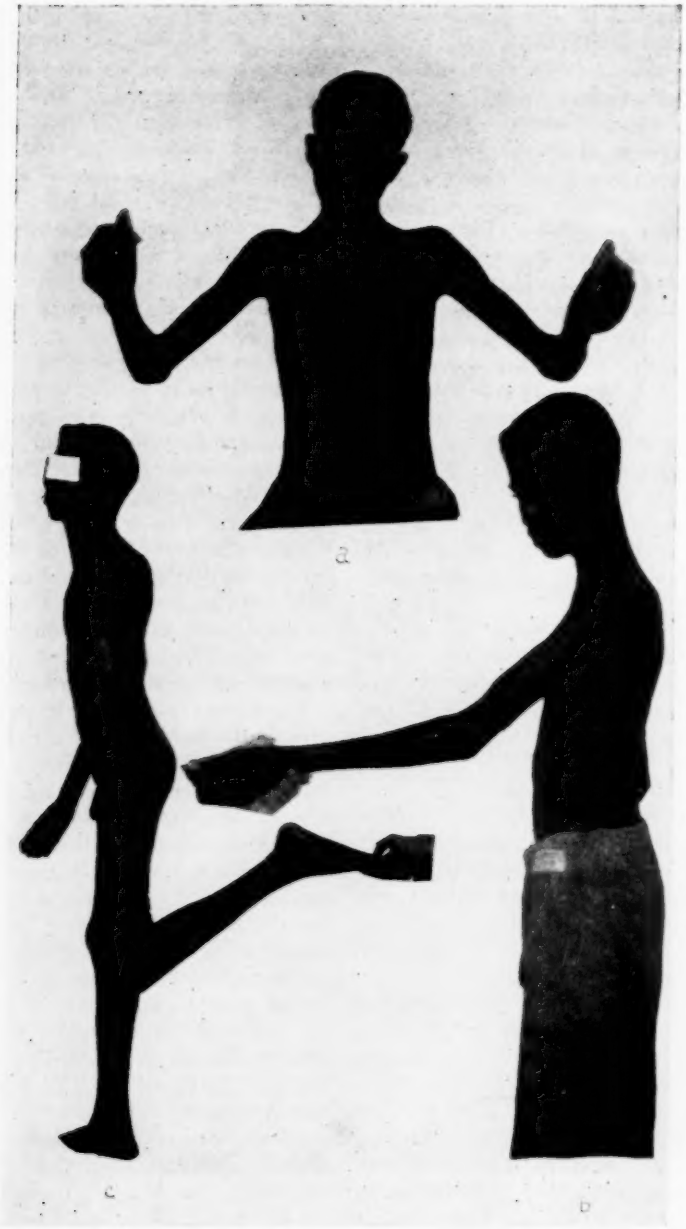

FIG. 1. Three views illustrating the impairment of muscle function; (a) showing maximum abduction of arms, (b) maximum extension of elbows, and (c) maximum flexion of the knee possible with force.

ish in color with their central portions semifluid in consistency and of a turbid, greenish color. The liver and spleen were larger than normal, their respective weights being 1860 and 230 gm. There was one small area of caseous necrosis in the spleen. No abnormal changes were noted in the kidneys, stomach, adrenals, pancreas, intestines, testicles, and urinary bladder. Permission was not granted for examination of the brain and spinal cord.

Microscopic Findings. The consolidated area in the left lung and the lymph nodes of the hilus and mediastinum showed evidence of an acute tuberculous process in the form of miliary and conglomerate tubercles along with liquefaction necrosis, especially in the nodes. The myocardium was abnormal in that there was a slight increase in the size of the fibers with a more granular cytoplasm. There was also a slight increase in fibrous tissue and in this were found a few scattered mononuclear, inflammatory cells. Parenchymatous degeneration and hyperemia were noted in the kidneys.

The histological examination of the *voluntary muscles* resulted in extremely interesting findings. Prior to death, specimens were obtained from the soleus and quadriceps femoris muscles. At autopsy tissue was procured from the following muscles: rectus abdominis, psoas, iliacus, pectorals, sartorius, diaphragm, intercostals, and deltoid. On gross examination the muscles were distinctly lighter in color and had a somewhat greyish tint. On palpation they were firmer than normal and on section cut with increased resistance.

Microscopically, degenerative, inflammatory, and fibrous tissue changes were found (figures 2 and 3). The three types of change were present in

FIG. 2. Longitudinal section of the rectus abdominis muscle. Note the variation in size of the individual fibers, their complete destruction in some areas, and the marked infiltration with inflammatory cells.

all muscles, varying, however, in degree. In both longitudinal and cross sections the individual muscle fibers exhibited great variation in size, some of them appearing larger than normal, whereas others were reduced to as much as a fifth their normal diameter. In many fibers, all striations had disappeared while in others the longitudinal striations only were present with loss of the transverse ones, and *vice versa*. Hyaline degeneration and hydropic infiltration were commonly noted. Scattered throughout the muscle tissue were varying numbers of inflammatory cells and in certain areas they formed definite collections. In such areas the muscle tissue had undergone more or less complete degeneration. By far the larger number of these cells were of the lymphocytic group. A small number of plasma cells were present along with large endothelial cells and fibroblasts. Only

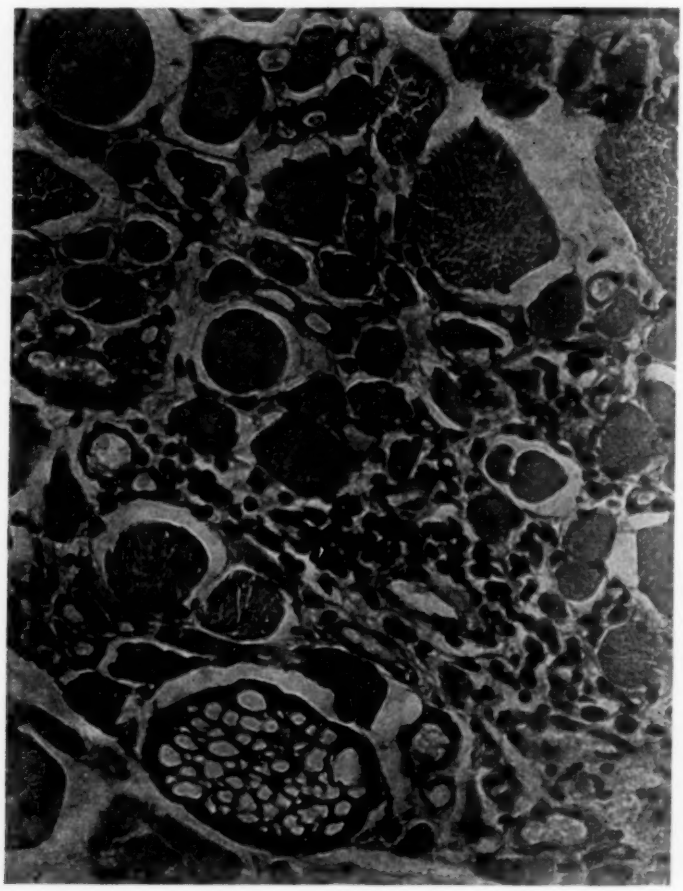

FIG. 3. Cross section of the sartorius muscle. Note the hyaline degeneration and the hydropic changes, the excess of fibrous tissue, and the collection of inflammatory cells around a small blood vessel.

an occasional polymorphonuclear cell was noted. Variable amounts of new fibrous tissue were found in different muscles, and constituted approximately 10 per cent of the muscle volume. This change was most marked in the iliacus, quadriceps femoris, rectus abdominis, and deltoid muscles. None of the fibrous tissue had reached the adult type. Microscopic study of the peripheral nerves revealed no departure from the normal. A more detailed description of the histopathology will be presented in a future communication.

The Clinical Picture

A summary of the clinical findings in the reported cases is outlined in table 1. Age and sex apparently play no part as predisposing factors in the causation of this disease. The youngest case occurred in an infant of 9 months, whereas the oldest was in a man of 48 years. Males and females appear to be equally affected. Our case is the only one reported occurring in the negro race.

The onset of the disease is insidious but once begun seems to progress fairly rapidly, the process requiring only a few months to cause definite impairment of muscle function. Batten's[7] case required 5 years to reach an advanced stage, whereas Hoover's[8] case was rendered an invalid in two years. In the case here reported the process developed more rapidly, producing invalidism in about 9 months. Previous diseases or infections were in some instances incriminated as factors in the causation of the muscular condition. The case of Burton, Cowan, and Miller[6] had had a pyelitis prior to the onset of symptoms and also frequent sore throats. In their case it is also interesting to note that there were exacerbations with each pregnancy. The questionable case reported by Gies[3] had a carbuncle on the back a year previously. Our case apparently had a quiescent pulmonary tuberculosis at the time of admission.

The presenting symptom in practically all of the cases was a feeling of stiffness in the extremities associated with inability to perform voluntary movements without clumsiness. This symptom became progressively worse as the disease advanced, ending eventually in marked limitation or complete loss of contractility of the involved muscles. Usually the first muscles to be affected are those of the extremities, most often the lower. The condition then gradually spreads to eventually involve nearly every muscle in the body. The muscles of the face and lips have apparently escaped in all cases that have been thus far described.

Considering the pathological changes present in the muscle tissue, one would expect pain to be a prominent and conspicuous symptom. On the contrary, it was entirely absent in the majority of the reported cases, and in those in which it was present, it occurred early in the disease and was a minor complaint of short duration. Janicke's[2] case had slight pain early in the course of the disease. In Hoover's[8] case and that reported by Gies[3] the muscles were said to be sensitive to pressure. Weakness and loss of weight were the outstanding constitutional symptoms. Fever was not mentioned as occurring in any of the cases.

The characteristic feel of the muscles on palpation is the outstanding

TABLE I
A Brief Summary of the Clinical Findings in the Reported Cases of Generalized Myositis Fibrosa

AUTHOR	AGE	SEX	RACE	PRESENTING SYMPTOM	FEVER	PAIN	EXTENT OF INVOLVEMENT	DURATION	SKIN LESIONS	OUTCOME	REMARKS
Janicke[2]	3	F	W	Swelling of the sternomastoid muscle and stiffness of the neck	None	Yes, early Not severe	Generalized, most marked in the neck, shoulder girdle, and arms	4 months	None	Improved some under treatment. Progressive, not followed	Under observation 4 months
Batten[7]	9 mo.	M	W	Stiffness of the arms and legs	None	None	Generalized, began in legs and abdomen	5 years	None	Death	Marked contractures
Burton,[6] Cowan, and Miller	25	F	W	Drawing up of the legs	None	None in the muscles, some in the shoulder	Generalized except muscles of face. Considerable atrophy	2 years	Skin of hands involved later	Living at present	Pyelitis and frequent sore throats. Worse during pregnancy
Hoover[3]	25	F	W		None	Muscles were sensitive to pressure	Generalized with marked atrophy	2 years	None	Death	Not proven microscopically
Gies[5] (atypical)	48	M	W	Pain in the rt. leg, later painful swelling of the thigh	None	Pain on palpation	Muscles of rt. thigh, later the calf muscles of same leg	Several months	Overlying skin like leather, adherent to muscles	Improved under treatment	Carbuncle a year before onset of illness
Gowers[8] (atypical)	36	F	W	Fatigue, pain in the back, and stiffness of the legs	None	Early but none later in the course of disease	Practically every muscle in body. Marked atrophy	1 year ?	Rash over arms and hands early	Not followed	Not proven microscopically. Loss of reflexes
Kreiss[4] (atypical)	30	M	W	Stiffness of the legs	None	None	Calf muscles of both legs	3 years	Skin over muscles hard and indurated	Improved under treatment. Not followed	Arthritis of both knees during illness Similar attack before
Schwab, Brindley, and Bodansky	14	M	B	Stiffness of the legs	None	None	Generalized except small muscles of face	1 year	None	Death	Pulmonary tuberculosis

diagnostic point. The muscles feel distinctly harder than normal and seem to be increased in consistency. To the palpating hand they impart the sensation of being edematous without any extension of the process to the subcutaneous tissues; they may be described as doughy or boggy. In the early stages of the disease the muscle volume is well preserved; in advanced stages there is a marked decrease in size and on palpation the muscles feel hard and boardlike. With the decrease in size of the muscles, resulting from contraction of scar tissue, there is an associated shortening which produces marked limitation of movement, a condition which eventually renders the patient completely helpless.

Diagnosis

Although positive diagnosis is possible only after microscopic examination of the muscles, their characteristic feel on palpation, the impairment of their function, the absence of pain, the lack of constitutional symptoms, and the chronic progressive nature of the condition constitute a clinical picture which can be confused with few other diseases. The absence of skin lesions readily differentiates myositis fibrosa from the chronic form of dermatomyositis. The primary progressive myopathies or muscular dystrophies offer little difficulty in the differential diagnosis. The familial manifestations, the tendency to a symmetrical involvement of muscle groups, and the marked atrophic, or in some instances the pseudohypertrophic, changes in the muscles are the outstanding points to be remembered. In the myopathies, weakness of the involved muscles is the outstanding symptom, whereas in generalized myositis fibrosa stiffness of the muscles is the predominant functional derangement.

Creatine Metabolism

A detailed study of the creatine metabolism having been reported in an earlier publication,[13] only a brief summary of the essential findings will be attempted in this connection. Derangement of the creatine-creatinine metabolism, particularly as regards the abnormal excretion of creatine in the urine, is a well-known manifestation of muscle disease. In the present case the creatinuria was particularly marked, more than 40 per cent of the so-called "total creatine"* being excreted as creatine, even on a meat-free diet. For the critical evaluation of this result two complicating factors should be borne in mind, the age of the patient and the co-existence of tuberculosis. As to the influence of age, there is inadequate information concerning the creatine metabolism in early adolescence, but such data as are available indicate that at the age of 14 and 15, creatinuria is either absent or of relatively small quantitative importance. Of perhaps greater significance is the influence of pulmonary tuberculosis. On the one hand, there are the careful observations of McClure[14] which demonstrate that creatinuria is not characteristic of this disease, and on the other hand there is the work of Thompson[15] which emphasizes that creatinuria is associated with pulmonary tuberculosis. It is perhaps

*This refers to the total excretion of creatine and creatinine, expressed in terms of creatinine.

judicious, therefore, to admit, for the present, the possibility that the age of the patient and the co-existing tuberculosis were contributory factors, but at the same time, it is quite obvious that the high grade of creatinuria was due primarily to the disease of the muscular system.

Since the creatine-creatinine metabolism reflects the endogenous metabolism, moderate variations in protein intake exert little, if any, effect in the normal individual, the creatinine excretion being maintained at a practically constant level. In contrast to this is the pronounced effect which the addition of meat to the diet produced in the case under consideration. With an increase in protein metabolism of approximately 70 per cent (from 10 gm. of urinary nitrogen in 24 hours to 17.07 gm.), the "total creatinine" was raised from 1.28 gm. to 2.25 gm., an increase of 1.27 gm., of which 0.99 gm. (78 per cent) was in the form of extra creatine.

Normal human voluntary muscle contains approximately 400 to 500 mg. of creatine per 100 gm. Apparently it is capable of storing creatine above this level, as shown experimentally by Chanutin[16] and as is evidenced by the fact that if creatine is fed a considerable portion is retained. The storage of creatine proceeds until a point is reached when more and more of the ingested creatine is excreted in the urine. Presumably a level of saturation exists and after it is attained, practically all of the ingested creatine, even in the normal individual, is promptly eliminated in the urine. It has been observed by one of us (M. B.), in unpublished experiments on himself, that when 10 gm. of creatine hydrate are ingested daily, the amount of creatine eliminated, though small at first, increases daily, but just as soon as the feedings are discontinued, creatinuria promptly disappears. The creatinine level of excretion, however, remains elevated for a considerable after-period, the extra creatinine owing its origin to the metabolism of a part of the extra creatine stored in the muscle (see also Benedict,[17] Rose *et al.*[18]). It is well known that this capacity for the storage of creatine is diminished in various muscle diseases, and therefore it was not surprising to find that this was true also in myositis fibrosa. Nevertheless, it was remarkable that there was almost complete inability to store the creatine for more than very short periods. On the administration of 1 gm. of creatine hydrate (equivalent to 0.758 gm. of creatine, in terms of creatinine), all was recovered within 24 hours, 92.1 per cent as creatine and the remainder as creatinine. On feeding 2 gm. of creatine hydrate, 91 per cent was recovered within 48 hours, and in a subsequent experiment, 96.5 per cent. When 5 gm. were fed, 91.73 per cent was recovered within 3 days. The obvious explanation is that the muscles possessed low saturation levels, so low in fact that even the creatine arising from the endogenous metabolism could not be retained sufficiently long to permit its normal metabolism to creatinine.

Analysis of various muscles, most of which were obtained soon after death, showed that their creatine content was abnormally low in all instances, and as has been stated else-

where,[13] a definite relationship was demonstrable between the creatine content and the degree of inflammation. Thus, the soleus which showed least inflammation contained the largest amount of creatine (324 mg. per 100 gm.), whereas the iliacus which showed the greatest degree of inflammation, contained, next to the diaphragm and myocardium, the least amount of creatine (160 mg.). It is worth noting that the diaphragm and heart muscle likewise showed definite pathological changes (degeneration, inflammation, fibrosis). The former contained 159 mg. of creatine per 100 gm. of tissue, as compared with normal values of 357 to 364 mg. obtained by one of us[19] with the same method of analysis (Ochoa and Valdecasas[20]). The myocardium also contained 159 mg. of creatine per 100 gm. Analysis of heart muscle in two cases of sudden accidental death yielded values of 265 and 285 mg., respectively.

The inescapable conclusion is that in myositis fibrosa a definite relation exists between the degree of inflammation and the amount of creatine which the muscle contains and which it is capable of storing. For purposes of comparison, the composition of diseased and normal muscle is summarized in Table II.

These results have a double significance. In the first place it is quite obvious that the creatine content of muscle in myositis fibrosa is much lower than normal; in the second place these closely approach the saturation level, whereas the data given for normal muscle are perhaps 10 to 30 per cent below the saturation level.

The uric acid content of the blood was relatively high, averaging 5.5 mg. per 100 c.c. in a series of six analyses of the blood taken at different times during the course of the disease. In part this may be attributed to the coexisting tuberculosis and in part to the somewhat exaggerated nuclear metabolism accompanying the destructive changes in the muscle.

From the standpoint of diagnosis, the marked creatinuria and the extremely low tolerance for exogenous creatine are considered to be valuable criteria, as is also the low creatine content of the muscle.

Prognosis and Treatment

A consideration of the small number of reported cases justifies the conclusion that the outlook is not hopeful.

Table II
The Creatine Content of Muscle Normally and in Myositis Fibrosa.
Muscle creatine in mg. per 100 gm. of fresh tissue*

Muscle	Number of subjects	Normal	Myositis fibrosa
Diaphragm	(3)	357,364,364	159
Myocardium	(2)	268,285	159
Deltoid	(2)	421,476	197
Sartorius	(1)	442	229
Intercostals	(2)	442,368	172
Psoas	(3)	476,483,476	204
Soleus	(1)	422	324

*Analysis by the method of Ochoa and Valdecasas.

The disease is progressive in nature. Its duration is variable. Batten's[7] case lived 5 years. The one reported by Burton, Cowan, and Miller[6,21] is living at the present time. Hoover's[8] case lived only two years. In the remainder of the cases the duration of life was not mentioned. In the later stages of the disease the patient's general health undergoes marked deterioration and death from some intercurrent infection is probable.

Little can be said as regards therapy. Drugs are of no value. Massage has been very beneficial in one of the reported cases.[6] Careful search for foci of infection should be made and when found such should be eradicated if possible as this measure might have some influence on the course of the disease. Massage, gymnastic exercises, and electrotherapy theoretically should be beneficial.

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Roentgenologic Diagnosis of Early Pulmonary Tuberculosis

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THE value of roentgen rays in the early diagnosis of pulmonary tuberculosis has been a theme of controversy in the past, on the assumption that it was a rival of the clinical examination. At present it is commonly granted without question that the two methods are complementary, mutually helpful, mutually corrective, and almost indispensable to each other. Accordingly, the practitioner of either may point out its advantages without seeming to boast, or admit its limitations without seeming to make reluctant concession.

With respect to the technic of roentgenologic examination of the lungs, it will be sufficient to say that roentgenoscopic study is inadequate either to disclose or exclude the presence of small tuberculous lesions, and that roentgenography, which preferably should be stereoscopic and rapid, is essential for decisive results. At The Mayo Clinic it has been found advantageous to make the roentgenograms at a distance of six feet, with high milliamperage and an exposure time of only a fraction of a second. By this means the blurring and obliterating effect of voluntary, respiratory or cardiac movement is precluded.

Obviously roentgen rays cannot reveal evidences of tuberculosis until demonstrable differences of density of the tissues have been produced by the infection. Rarely, cases with clinical manifestations suggestive of the disease give no roentgenologic signs. But the converse occurs far more often, and very many cases can be cited in which the affection was disclosed by roentgen examination when clinical symptoms and signs were vague and trivial, or absent altogether. Sampson and Brown[1] have said that in a surprisingly large number of cases, definite changes characteristic of tuberculosis are seen in the film long before definitely abnormal physical signs can be detected. They have stated, further, that among 1,367 consecutive cases at Trudeau Sanatorium, the physical signs in 32 per cent were either absent or so slight that the diagnosis was established entirely, or in large part, from study of the films. Webb[2] has said, succinctly, that roentgenologic examination is the only meth-

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od available for detecting early pulmonary tuberculosis.

Early Tuberculosis of Adults

Almost all cases of incipient tuberculosis of adults may be divided into two groups. In the first group, which comprises by far the greater number, the earliest significant manifestation is a relatively faint shadow in an upper lobe, more often that of the right lung (figures 1*a* and *b*). As seen stereoscopically, the dense region is more or less conical; on the single film it appears to be fan-shaped. Its base is at the periphery of the lung, and is often directed toward the axilla; its apex points toward the hilum. It lies obliquely below the clavicle, usually in the first interspace, occasionally in the second, and its long axis corresponds to an external twig of the ascending branch of the main bronchus. On close inspection, the shadow is seen to be made up of a confused network of delicate lines enveloped in a filmy veil. Its appearance has been likened aptly to that of a web spun by caterpillars about an outer branch of a tree.

In the second group, the lesions are likewise situated in the outer parenchymatous portion of the subclavicular region but are more or less spherical in form (figure 2*a*). More often they are multiple, but they may be single. When multiple they are grouped, but in such variable degrees of proximity to each other that they may plainly be discrete or apparently confluent. Their size varies from a diameter of 1 or 2 mm. to several centimeters, and multiple foci are likely to be diverse in size. Their shadows are faint, although denser at the center than at the periphery, the latter being especially hazy and indistinct.

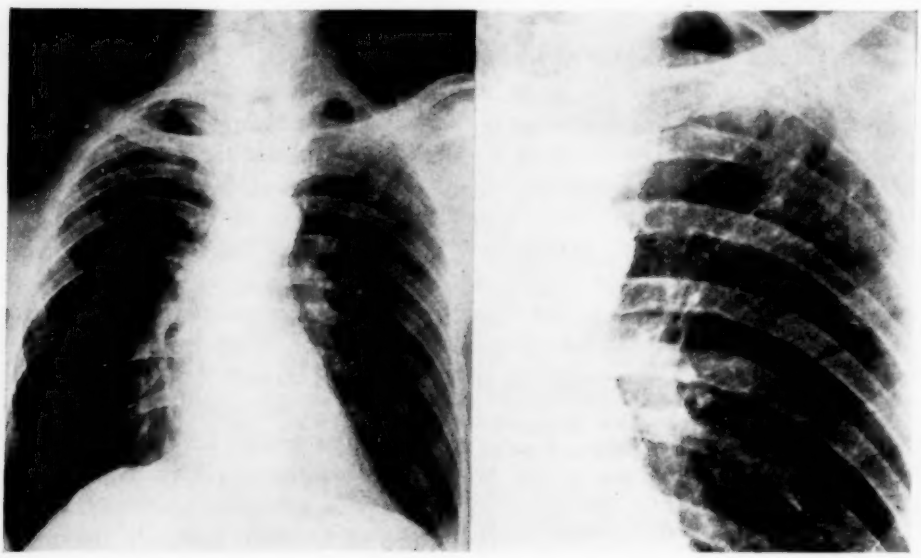

Fig. 1*a*. Early, active, fan-shaped lesion in left upper lobe; *b*, close-up of roentgenogram *a* for clearer depiction of lesion.

Common to both groups is an accentuation of the bronchovascular trunk leading from the affected region to the hilum. Occasionally the ribs on the affected side descend more steeply, and the intercostal spaces are narrowed, although these phenomena more often accompany advanced than early disease. Not infrequently the unaffected lung appears to be more brilliantly transradiant than normally. Roentgenoscopically, respiratory excursion of the diaphragm on the diseased side is likely to be restricted, and the apex is often less bright than its fellow. But restriction of diaphragmatic movement occurs in many diseases other than tuberculosis, and apical darkening not only has other pathologic causes but is often devoid of significance. Lesions in the apical field above the clavicle are rarely encountered early in tuberculosis; when they are present the disease almost invariably is well advanced, and then its manifestations below the clavicle are more conspicuous.

In the differential diagnosis four prime characteristics of early tuberculosis are to be kept in mind, namely, its situation below the clavicle and in the outer parenchyma of an upper lobe; the roughly conical or spherical form of the lesions, the softness and lack of marginal definition of the shadows, and the accentuation of the tributary bronchovascular stem. Few of the simulants have all these characteristics. Among such simulants to be considered are: bronchiectasis, malignant metastasis, the lateral border of an azygos lobe, shadows from extraneous causes, accentuation of bronchovascular markings without correspond-

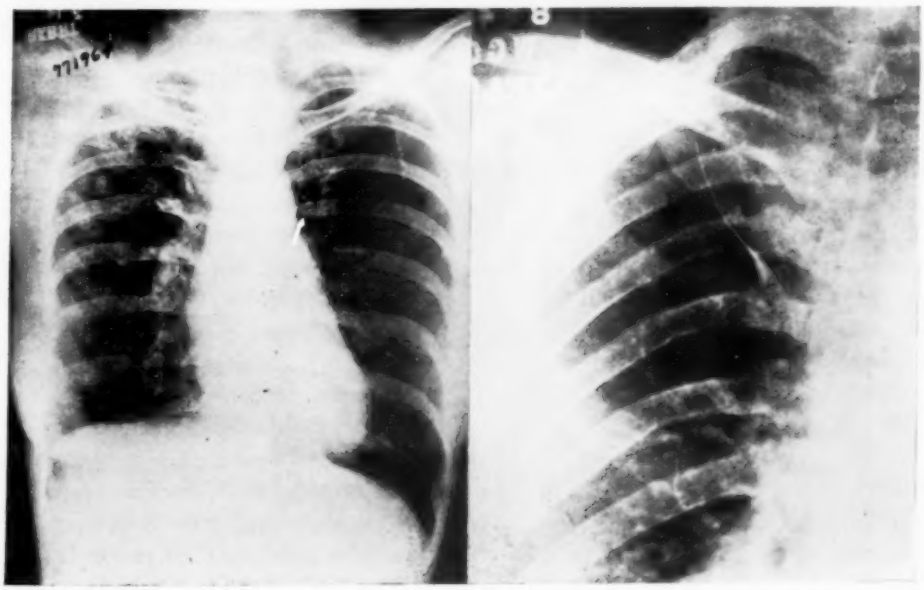

FIG. 2*a*. Nodular type of lesions in right upper lobe; *b*, shadow resembling an inverted comma and representing the outer border of an azygos lobe.

ing parenchymal shadows, localized simple pneumonitis, and small, healed, tuberculous lesions.

Bronchiectasis in an upper lobe is usually depicted as a mottled, irregularly triangular shadow with its apex toward the hilum. However, bronchiectasis seldom affects upper bronchi; even in this event the lesion is essentially bronchial, and, although the corresponding parenchymal alveoli may be atelectatic, the more striking shadows are central rather than peripheral.

A malignant metastatic nodule in the infraclavicular region may imitate an early conglomerate tubercle. But metastatic nodules are most often numerous when discovered, and are likely to be widely scattered in several lobes. Further, a metastatic nodule is likely to be more regularly spherical, denser, and more sharply defined than a tuberculous nodule. An azygos lobe in the superior mesial portion of the right lung is not altogether rare (figure 2*b*). Its lateral border is represented by a curving shadow resembling an inverted and elongated comma. Since an azygos lobe is somewhat unusual, this shadow may be mistaken for an indication of disease, and its situation may suggest the thought of tuberculosis, but other essential features of tuberculosis are lacking. During the process of roentgenography, certain patients, especially women, are sometimes permitted to wear a cape, or other light clothing which may produce a faint shadow over the apical region. On stereoscopic view the cause of the shadow should be apparent, but it is safer to insist that the patient's chest invariably be bared.

An hypothesis that tuberculosis of adults habitually arises from recrudescence of the primary infection acquired in childhood by retrograde extension from the hilar nodes into the lymphatic channels, especially the upper trunks, and thence into the parenchyma of the lung, has been responsible for many wrong diagnoses. This hypothesis was popularized by certain continental roentgenologists, and until a few years ago was widely accepted. Intensification of the hilar shadow and of the principal vascular markings, together with a socalled beaded or varicose appearance of the trunks, was deemed sufficient warrant for the diagnosis of "peribronchial tuberculosis". In the course of time, however, it was learned that frank tuberculosis almost never developed in cases in which such manifestations occurred, and that these appearances are often found in persons in robust health. Then the phrase, "peribronchial thickening" came into frequent use; but this expression is equivocal and so susceptible of erroneous interpretation that it is falling into disfavor. At all events, few roentgenologists will take responsibility for even a tentative diagnosis of tuberculosis unless the abnormal shadows extend to the peripheral portion of the lung, where shadows of the vessels are not normally visible.

Restricted, simple pneumonitis in an upper lobe, resulting from a cold or other ordinary infection, is a highly deceptive simulant of early tuberculosis. The morbid change may appear as a faintly shadowed conical segment, probably representing congestion chiefly, or as a small mottled patch depicting narrowly localized bronchopneumonia. In either instance the situation

and general character of the shadow, together with the intensification of the corresponding vascular marking, are identical with those of one or the other type of early tuberculous lesion, and the roentgenologist will be inclined consistently to make the latter diagnosis, at least provisionally. It is in such cases that the clinician can avert a wrong diagnosis by temporarily withholding final judgment, observing the course of the disease, and sending the patient for reëxamination later. Fortunately, the acute, simple, pulmonary infections usually attack lower lobes, and invasion restricted to an upper lobe is rare, but it should be kept in mind when colds, pneumonia or influenza are prevalent.

Activity

Inability of the roentgenologist to distinguish with precision between arrested and active lesions is an important source of error. The majority of healed lesions are dense and sharply delimited from the normal tissue (figure 3*a*); they are likely to be accompanied by calcified lymph nodes at the hilum or elsewhere; often the interlobar pleura, especially that of the right upper interlobar fissure, is visibly thickened. Conversely, most of the early active lesions cast thin shadows which merge indefinably with those of the normal tissue, and they are seldom associated with calcified nodes or interlobar thickening(figures 1, *a* and *b* and 2*a*). But between the cases which are manifestly active and those which are plainly inactive, are many in which the degree of density and of marginal definition is hard to evaluate, and decision depends too largely on the personal equation of the examiner. Sometimes,

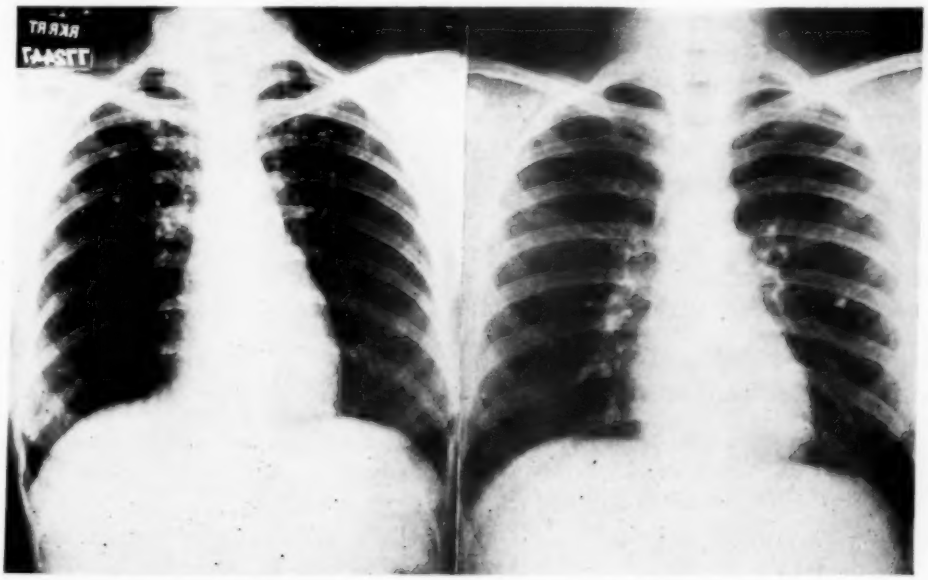

Fig. 3*a*. Healed tuberculous lesions in the upper lobes of both lungs; *b*, healed Ghon tubercle in seventh interspace, posteriorly, of left lung. Calcification of the regional lymph nodes may be noted.

also, the roentgenologic indexes of activity or inactivity are not reliable; an apparent perifocal haziness may be the result of movement; lesions remote from the film appear less dense and less clearly defined than they would if near the film; density and marginal definition vary with the quality of the rays. For these reasons the roentgenologic opinion should always be subject to clinical review. As a single test of activity the roentgenologic examination is probably equal to any other; but no single test is a sufficient basis for such a momentous decision.

In very rare instances tuberculosis of adults is limited to a lower lobe or to the circumhilar region, and its manifestations are identical with those often observed in children. Although the pathologic changes are obvious at an early stage, the roentgenologist cannot logically attribute them to tuberculosis. In fact, when abnormal shadows are found only in a middle or lower lobe, the presumption is strong that they are not due to tuberculosis but to some other disease. As a rule, the appearance is suggestive of restricted, simple bronchopneumonia, and is so interpreted. The symptoms and physical signs are also so contradictory or confusing that usually the proper diagnosis is made only after a period of observation.

Tuberculosis of Children

Early tuberculosis of children has many points of difference from that of adults: it is commonly accepted that, by the time puberty is reached, virtually all children within the precincts of civilization have been infected with the bacillus of tuberculosis, and Ghon's theory that the initial pulmonary lesion arises in the parenchyma is generally endorsed. But wherever the portal of entry may have been, the intrathoracic lymph nodes are by far the most common manifest site of reaction to this infection. Subsequently any of several results may follow: (1) healing or arrest, as occurs in the great majority of cases; (2) development of clinically important, primary, focal tuberculosis directly or indirectly from the parenchymatous or nodal focus; (3) development of miliary tuberculosis, and (4) development of an adult type of tuberculosis from new, secondary infection after subsidence of the primary infection.

Since primary tuberculous infection in children is the rule, roentgenologic confirmation of the fact, even if feasible, would be superfluous. A few roentgenologists have interested themselves in the Ghon focus. This is commonly small, situated in any lobe, whether upper or lower, and revealed as a variously shaped shadow in the parenchyma, but only after the lesion has passed its earlier stages (figure 3, *b*). Such a shadow is likely to be found in the roentgenogram of any child's chest, but identification of the shadow as that of a Ghon focus is necessarily uncertain. A roentgenologic diagnosis of tuberculous mediastinal lymphadenopathy is also insecure. In roentgenograms of children who have no clinical evidence of disease, the mediastinal shadow is usually wide, the lymph nodes about the hilum on both sides are frequently depicted, and the larger vascular markings seem to be accentuated. If the subject were an adult the picture would be abnormal, but since it is usual in

childhood it must be rated as normal. Often, especially in younger children, the adenopathy is more pronounced; the mediastinal shadow is vastly widened bilaterally, and its borders may be straight, convex, or polycyclic. However, identical manifestations may follow various infections of childhood, especially measles or whooping cough, and may persist for many weeks. In any case, therefore, the cause of the adenopathy is a problem to be solved by the clinician rather than the roentgenologist. Even when the primary infection in children has given rise to early parenchymal disease of actual or potential moment, difficulties in its roentgenologic recognition persist. The lesion may appear in any of the lobes, but it has a predilection for the circumhilar region or for the lower portion of the lobe invaded. Its shadow is of sufficient size and density to be obvious and may be somewhat fan-shaped, or irregular, or, if at the hilum, irregularly hemispherical. Wherever it may be, it inclines to a central, rather than a definitely peripheral situation. The mediastinal shadow is widened, perhaps lobulated, and the radicular markings are emphasized. On the whole, the picture is rather plainly that of localized pneumonitis, but whether simple or tuberculous can scarcely be determined positively from the roentgenologic appearance alone. If the examiner attempts to carry his interpretation farther he will be likely to consider bronchopneumonia, tuberculosis, and lobar pneumonia, the order of choice varying according to his most impressive experience and the more striking features of the case at hand. Always, if he is duly cautious, he will make his diagnosis conditional on clinical confirmation and will suggest the various alternatives. The clinician also is often hampered by the indefinite or eccentric physical signs and the difficulty of obtaining satisfactory sputum tests, so that extended observation may be required for final decision.

Miliary Tuberculosis

Inasmuch as diffuse, hematogenous, miliary tuberculosis often arises from a small, hidden pulmonary or nodal focus, or from one which is remote and unsuspected, it is perhaps entitled, in such circumstances, to inclusion among early forms of the disease. In the absence of definite knowledge of an antecedent focus, an independent clinical diagnosis is almost impossible, whereas roentgen rays usually will reveal the condition and often identify it positively. During the earliest stages of pulmonary invasion roentgen rays may fail to disclose any evidence of the disease, and death may occur, especially of infants, before any changes can be demonstrated on the film. Notwithstanding such exceptions, roentgen rays in the majority of cases give a definite picture and one which is perhaps the most characteristic of any variety of tuberculosis. At first, mere veiling of the pulmonary markings may be seen, but shortly the tubercles also are visible as a multitude of minute flecks distributed more or less evenly over all parts of both lungs. The resulting pulmonary shadow has been described variously as having a granular, mottled marbled, or stippled appearance. To me it seems to resemble a sponge, the texture of which

varies from exceedingly fine to moderately coarse (figure 4).

Despite the almost pathognomonic evidence afforded by roentgen examination, dependence on it should not be absolute. Of diseases which may enter into the roentgenologic differential diagnosis the most common are malignant miliary metastasis and pneumonoconiosis, particularly that produced by organic dust. Their chief marks of distinction are the following: Miliary metastatic lesions, although small, are very diverse in size, commonly denser than miliary tubercles, and most numerous in the lower two-thirds of the lung. Pneumonoconiosis ordinarily spares the apexes and is most manifest about the hilum; the individual lesions are likely to be larger, more irregular in size and shape, and denser than miliary tubercles. Accordingly, the examiner usually can venture a specific diagnosis, but prudence demands that it have clinical approval.

Comment

I am aware that this appraisal of the capabilities of the roentgen rays in the diagnosis of early pulmonary tubercu-

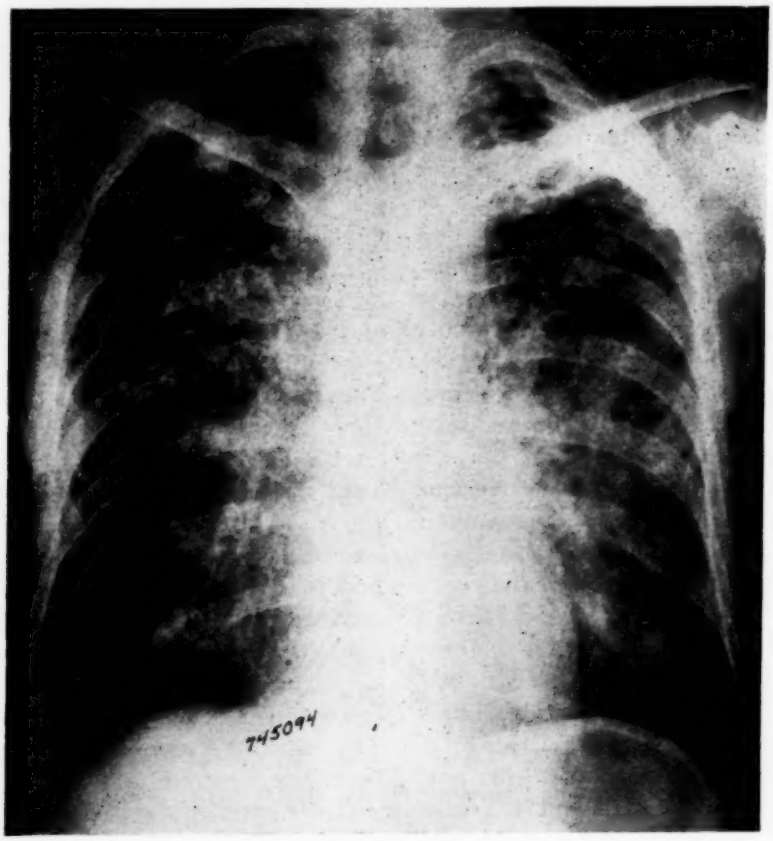

Fig. 4. Miliary tuberculosis. The lesions are rather advanced but illustrate the sponge-like appearance they produce.

losis may seem unduly conservative to many who have implicit confidence in the roentgenologic examination, or may appear unduly liberal to the smaller number who are skeptical of the method. To the skeptics it may be pointed out again that without employment of roentgen rays as a routine, most of the truly early cases will escape recognition. Indeed, as a single rapid method for the definite revelation of the lesion, the determination of its probable nature, and even the estimation of its activity, I do believe that the roentgenologic examination is not surpassed by any other. Nevertheless, I have dwelt on its limitations because there is a prevalent tendency toward unquestioning reliance on laboratory tests. Although this flattering faith has been a stimulus to roentgenologic progress, it has sometimes led the roentgenologist into incautious or unqualified interpretations. It has been difficult to learn that the normal chest has a wide range of variations, and that not all adventitious shadows are significant of present disease. Consequently the novice, and sometimes even the expert, are inclined to the diagnosis of tuberculosis when none exists. Many sound or nontuberculous persons have been sent to sanitariums on the basis of a roentgenologic opinion which the clinician failed to verify. In short, while the roentgen rays have brilliantly illuminated the field, the clinician still is obliged to study all the landmarks critically before he assents to a diagnosis so grave as that of tuberculosis.

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Medical Men Who Have Attained Fame in Other Fields of Endeavor

III. Medical Humorists. IV. Medical Men as Inventors. V. Medical Men as Explorers

By Ernest Weinfield, B.S., M.D., *New Orleans, La.*

III. Medical Humorists

SAAVEDRA Miguel de Cervantes (1547-1616) the greatest of Spanish writers, bent upon the alleviation of all the ills of mankind, was a doctor in very truth. He early commenced writing verses, and his pastoral, "Filena", attracted the attention of Cardinal Acquaviva whom he accompanied to Italy as page. In 1570 when serving in the war against the Turks and African corsairs, he lost the use of his left hand. In 1583 he retired from service and recommenced his literary work, publishing in 1584 his pastoral "Galatea". He lived by writing for the stage, to which he contributed between twenty and thirty plays, only two of which have survived. In 1605 he produced the first part of Don Quixote and it had a hearty reception from the beginning among the populace, though not among the cultured classes. Between 1613 and his death were published his twelve "Exemplary Tales", "Journey to Parnassus" and eight new dramas. The second part of "Don Quixote" was also completed during these years and it is the masterpiece through which his fame lives.

Francois Rabelais (1490-1553) was at first a monk, but having been punished for some indecorous behavior, he quitted the Benedictine order, studied medicine at Montpellier, and later practiced as a physician. In 1532 he went to Lyons as hospital physician. In 1536 Rabelais obtained from the pope absolution for the violation of his monastic vows and permission to practice medicine and to hold benefices. During most of 1546 and part of 1547 he was physician to the town of Metz. Rabelais was the author of several books but the only one by which he is known is the romance called, "The Lives, Heroic Deeds, and Sayings of Gargantua and Pantegruel", an extravagant satire upon monks, priests, popes and pedants, in which much obscenity

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Note by Editor: Previous items in this series were I. Medical Men as Musicians, Ann. Int. Med., 1930, iii, 1047-1054; and II. Medical Poets, Ann. Int. Med., 1930, iii, 1279-1287. Dr. Weinfield had planned a group of articles covering the outstanding contributions of medical men to all the non-medical arts and sciences. He left much material in well-organized form at the time of his death. The present sections are selected from that material, made available through the courtesy of Mrs. Weinfield.

and absurdity are blended with learning, wit and humor. Rabelais made one of the first Latin translations of the aphorisms of Hippocrates (Lyons, 1532). He was the first to lecture on medicine at Montpellier with the Greek text before him.

Tobias Smollet (1721-1771) was educated in Dumbarton and at Glasgow Universities where he studied medicine. After some years of apprenticeship with a surgeon, a Dr. John Gordon, he went to London. His interest, however, was rather in literature than in surgery and in 1739 made an attempt, but was unsuccessful in having his tragedy "The Regicide" performed. After some years' service as surgeon's mate on board the Cumberland, he returned to England and again took up literature. The first of his picaresque novels, "Roderick Random", appeared in 1748, and its success was immediate and great. His second novel, "The Adventures of Peregrine Pickle" (1751), was even more successful. He practiced as a physician at Bath, and in 1753 returned to London, gave himself up to literature and wrote "Ferdinand Count Fathoms". He made a lively but inaccurate version of "Don Quixote" (1755), published a "History of England" in four volumes (1757), and "Sir Lancelot Greaves" (1760), a weak imitation of "Don Quixote". After a tour of Italy Smollet published his "Travels". In 1769 he produced his coarse satire "The History and Adventure of an Atom", dealing with politics in England during the previous fifteen years. In 1771 he wrote his masterpiece, "The Expedition of Humphrey Clinker".

Oliver Goldsmith* (1728-1774) went to Edinburgh to study medicine. Here he remained eighteen months, during which time he acquired some slight knowledge of chemistry and natural history. At the end of this period he went to Leyden, where he studied for nearly a year, and afterward he wandered over a large part of France, Germany, Switzerland and Italy. He had no money to pay his expenses during his walking tour, but his kindliness and humor won him friends everywhere, and his skillful playing of the flute gained him a scanty living. While at Padua he took a medical degree. He returned to England in 1756 where he commenced practice as a physician, in which he was unsuccessful. He then entered the field of letters and his first work to attract attention was an "Inquiry into the Present State of Polite Learning in Europe" (1759). To this succeeded, "The Citizen of the World", a "Life of Beau Nash" and a "History of England". Becoming acquainted with Dr. Johnson in 1761, the latter introduced Goldsmith to the Literary Club. In 1764 appeared "The Traveler" which at once placed Goldsmith in the front rank of English authors. Two years afterward appeared the "Vicar of Wakefield". Following in rapid succession came "The Good-Natured Man" (1767), "History of Rome" (1768) and the exquisite poem, "The Deserted Village" (1769). In 1773, his immortal comedy of "She Stoops to Conquer or Mistakes of a Night" took the public by storm. His

*See also Roddis, L. H.: Oliver Goldsmith, M.D., Ann. Int. Med., 1932, v, 1427-1436. —Editor.]

other works are "Grecian History" (1774), "Retaliation" a serio-comic poem (1774), and "History of Animated Nature" which he did not live to finish. Washington Irving has written a remarkably sympathetic biography of Goldsmith.

Charles Jones Lever (1806-72) graduated in arts at Trinity College, Dublin, in 1827, and in medicine in 1831, taking his doctor's degree a little later at Göttingen. He then returned to Ireland to practice. In 1834, he contributed his first paper to the newly-started "Dublin University Magazine" of which he became editor in 1842. The first chapter of "Harry Lorrequer" appeared in that magazine in 1837. Meanwhile he was attached as physician to the British legation at Brussels, where he practiced for three years. During his three years editorship of the "Dublin University Magazine" he resided near Dublin, and afterwards lived on the Continent, devoting himself to fiction writing. "Charles O'Malley", "Tom Burke", and "Jack Hinton" are representative novels, and in a class by themselves. He also wrote "Arthur O'Leary" and "Roland Cashel".

Oliver Wendell Holmes (1809-94) graduated from Harvard in 1829, in the class which he himself made famous in later years by his yearly poems at its reunions. After studying law for a time, he turned to medicine, at first with little seriousness. He became deeply interested, however, and the years during which he studied medicine in Paris were most industriously spent. His degree of M.D. was received in 1836 and he settled down to practice medicine in Boston. While yet in college, Holmes wrote numerous poems including "The Spectre Pig" and "The Height of the Ridiculous". Following his graduation from Harvard he wrote "Old Ironsides". In 1839 he was given a position as lecturer on anatomy and physiology in Dartmouth College and in 1847 gave up his practice entirely and became professor of anatomy at the Harvard Medical School, a position he filled until 1882. Various medical papers, some of which were of great importance in the profession, such as "On the Contagiousness of Puerperal Fever" (1843) and "Puerperal Fever as a Private Pestilence" (1855) came from Holmes' pen from time to time, and his poems written to celebrate every special occasion in his beloved city of Boston made him locally famous as a wit. It was not until the founding of the "Atlantic Monthly" in 1857, however, that Holmes became widely famous. He contributed his papers "The Autocrat of the Breakfast Table" which are up to the present day considered his masterpiece. His first series was followed by "The Professor at the Breakfast Table" and later by "The Poet at the Breakfast Table". He wrote three novels, "Elsie Venner, A Romance of Destiny", "The Guardian Angel" and "A Mortal Antipathy". After a visit to Europe in 1886 appeared "Our Hundred Days in Europe" and when Holmes was eighty, he wrote a final autocrat series under the title of "Over the Teacups". Among Holmes' best poems may be mentioned "The Chambered Nautilus", "The Last Leaf", and the "The Wonderful One-Hoss Shay".

IV. Medical Men as Inventors

Joseph Ignace Guillotine (1738-1814) went to Paris, where he practiced medicine with such success as to win recognition as one of the foremost physicians of the day. When the Revolution broke out, he became one of its ardent supporters and suggested that a decapitating machine be used in inflicting the death penalty. After the rise of Napoleon he resumed his practice in Paris where he was one of the earliest and most earnest champions of vaccination.

Richard Jordan Gatling (1818-1903) graduated from the Ohio Medical College in 1850. He assisted his father in perfecting a machine for sowing cotton seed and another for thinning out cotton plants. In 1850 he invented a double acting hemp brake and in 1857 a steam plow. His principal invention and the one by which he became famous was the revolving machine gun which bears his name (1861). In 1886 he invented a new gun metal of steel and aluminum.

Rufus Henry Gilbert (1832-85), after graduating at the College of Physicians and Surgeons in New York City, began medical practice at Corning, N. Y. At the outbreak of the Civil War he became a surgeon in the Duryea Zouaves (Fifth New York Infantry) and rose to be medical director and superintendent of the Central Railroad of New Jersey. Gilbert was appointed superintendent and medical director of the United States army hospitals. Owing to the failure of his health during the war he abandoned his profession and engaged in the railroad business, making a special study of the needs of rapid transit in New York. The result was the erection (1878) of the Sixth Avenue Elevated Railway in that city.

Alexander Graham Bell (1847-1922) received his medical education at the University College, London, and the London University. In Elgin he was for two years resident master and teacher of elocution and music. He was greatly interested in his father's system of instruction of the deaf and dumb and in 1872 he became professor of vocal physiology in Boston University. Among his most important inventions are the harmonic multiple telegraph (1874), the fundamental method that underlies the electric transmission of speech to any part of the world (1895); the magneto-electric speaking telephone (1875); the photophone for transmitting speech and other sounds to a distance by means of a beam of light (1880); an induction-balance with magneto-electric telephone for painlessly locating bullets or other metallic masses lodged in the human body (1881); the telephone probe to determine the position of bullets or other metallic masses lodged in the human body (1881); the spectrophone for determining the range of audibility of different substances in the spectrum (1881); joint invention of the graphophone; tetrahedral kites (1903); joint inventor in a number of improvements designed to promote aerial locomotion.

Carl Auer von Welsbach (1858-) attended the University of Vienna, and at Heidelberg (1880-82). In 1885 he discovered two new elements, "praseodymium" and "neodymium" and invented the incandescent gas burner, known by his name. He invented the

osmium incandescent electric lamp in 1898, and in 1907 discovered another new element known as "lutecium".

V. Medical Men as Explorers

David Livingstone (1813-73) was a graduate of the Faculty of Physicians and Surgeons of Glasgow. Under the auspices of the London Missionary Society he went in 1840 as medical missionary to South Africa. He discovered the Victoria Falls of the Zambezi in 1855. From 1858 until his death, he prosecuted his labors as explorer and missionary in Africa.

Elisha Kent Kane (1820-57) obtained the degree of M.D. at the University of Pennsylvania in 1842. He was attached as surgeon to the American mission to China and afterwards visited India, Egypt, and Greece. In 1850 Kane joined the Grinnell Expedition, as medical and scientific member, in the unsuccessful search for Sir John Franklin. His fame as an Arctic explorer rests on his second expedition, in search of Franklin in 1853-55. He sailed from New York in the brig "Advance" and reached lat. 78° 41′ N., the point farthest north attained up to that time by a sailing vessel.

Hays, who accompanied Kane, was also a physician.

Sir Wilfred Thomason Grenfell (1865-) graduated in medicine at London Hospital. In 1889, under the auspices of the Royal National Mission to Deep Sea Fishermen, he equipped a hospital ship to accompany the fishing fleets from the North Sea ports to Iceland. Three years later he went to Labrador and Newfoundland, where he established hospitals at many points along the coast. He wrote many books, chief of which are "Off the Rocks" (1906); "Down to the Sea" (1910); "Down North on the Labrador" (1911); "The Adventures of Life" (1912).

Jean Baptiste Etienne Auguste Charcot (1867-) was educated in Paris and after graduating in medicine, was attached to several important hospitals. In 1903 he began a series of antarctic explorations in the region of the South Pole. His published writings are "France at the South Pole" and "Around the South Pole".

Editorial

THE COMPARATIVE COST OF MEDICAL JOURNALS

Faced with yearly deficits in the portion of its budget devoted to the purchase of medical periodicals, the Library of the College of Physicians and Surgeons of Columbia University undertook an analytical study[1] of the costs of the various medical journals purchased. It was soon found that the deficits were due in large measure to the impossibility of accurately determining the cost of certain periodicals in advance. While no such difficulty was encountered with the allowances for American, British or French journals, the estimates for German periodicals were frequently inaccurate. Many German medical publications are priced by the volume or by the part as issued; and in these days when there is such an urge to publish, the temptation to multiply volumes is very great. It is unfortunate that the German publishers do not adopt the fixed annual subscription plan. This would make it possible to regulate production and curb extravagant charges. Not only are several volumes crowded into one year but supplementary volumes, Festschriften, Beihefte, Abhandlungen, etc., are added, all at further increase in cost. The rank and file of American medical readers must look to our libraries for these journals, and the libraries are naturally very desirous that their files should be kept intact. Present prices, however, are forcing cancellation in many instances, and with cancellations, other things being equal, prices must rise still higher for the cost of production is distributed over a smaller number of purchasers. During the year 1930-1931 the cost of certain important German medical periodicals was as follows: Archiv. f. Dermatologie, $92.25; Archiv f. Psychiatrie, $103.57; Deutsche Zeitschrift f. Chirurgie, $62.88; Strahlentherapie, $70.23; Virchow's Archiv, $111.98; and Zeitschrift f. klinische Medizin, $74.55. If domestic subscription lists have fallen so low that foreign subscribers must be asked to pay such prices as those just quoted, it is high time that production costs were cut drastically. Material must be condensed and the number of pages and volumes reduced. Otherwise the present trend will prove to be suicidal. It would be a deplorable situation if the sequence of truly great journals with many decades of usefulness should be interrupted. Not all German medical periodicals fall into the price range quoted but the average annual cost of 88 of them received by the Library of the College of Physicians and Surgeons was $36.41, while the average annual cost of 73 items of American origin was $7.91.

[1] ROBERT, ALFRED L., and SCHALTENBERG, HANS H.: The comparative cost of medical journals, BULL. MED. LIBRARY ASSOC., 1932, n.s. xx, 140-155.

The cost per page affords a method for the private subscriber as well as for the library to arrive at comparative costs of periodicals. For a number of reasons this method is crude and inaccurate. Differences in size of page, quality of paper, number and type of illustrations and in the extent to which the subscription list is relieved of the necessity of carrying the full cost of production by endowments, subsidies, or income from advertising are factors —and there are many others—which enter into the cost per page. Since many of the operations in the production of a periodical are constant regardless of the number of copies issued, it follows that the cost per page can be lowered, either by reduction in the subscription price or by increase in the number of pages, as the list of subscribers grows. It is not surprising, therefore, that the Journal of the American Medical Association had a per page cost in 1930-1931 of but 0.16 cents. Returning to the national groups previously considered, the average cost per page of 88 German medical periodicals was found to be 1.88 cents, while 73 American items had an average cost per page of 0.58 cents. It is a source of satisfaction to find that the ANNALS OF INTERNAL MEDICINE was placed in the hands of its readers during that year at a cost of but 0.43 cents per page, well below the average of the American journals as a group. Even then it is not the lowest priced journal in its field, although it might be found to be such if the unit cost were weighted in respect to number and quality of illustrations used. The ANNALS will never be published for profit. In fact, it has required a subsidy from the general funds of the American College of Physicians in practically every year of its existence. With a growing subscription list, however, it should soon be not only self-sustaining but also in position to reduce the cost per page as well. That the price of subscriptions to our American journals is based on an annual volume assures the purchaser a fixed limit to his obligation and necessitates a fixed limit to the total output. It would be to the ultimate advantage of all medical libraries and of their patrons if the application of this system were made worldwide.

Abstracts

Coarctation of the Aorta with Report of Three Cases. By G. F. STRONG, M.D. (Canad. Med. Assoc. Jr., 1932, xxvii, 15-19.)

The term 'coarctation' is applied to both a narrowing and a complete obliteration of the lumen of the aorta at or near the insertion of the ligamentum arteriosum—the obliterated ductus Botalli. This is found in the descending limb of the aortic arch distal to the origin of the subclavian artery. Of the three examples described in this paper, in the first, which occurred in a man 19 years of age, the occlusion was complete and death resulted from rupture of the aorta. The second was in a man, aged 38 years, in whom the lumen of the aorta was reduced to a diameter of about 2 mm., death being due to cardiac decompensation. The third patient was a girl, aged 12 years. The diameter of the aorta at the point of narrowing was but 0.8 mm. Death was due to

chronic nephritis and pneumonia. No one of these cases was diagnosed as to the coarctation during life. With the condition borne in mind, such findings as cardiac hypertrophy, widening of the aortic arch, evidences of arterial collateral circulation, retarded femoral pulse, and a systolic murmur over the major collateral trunks may make the diagnosis possible.

The Effect of Cabbage Feeding on the Morphology of the Thyroid of Rabbits. By ISOLDE T. ZECKWER, M.D. (Am. Jr. Path., 1932, viii, 235-244.

Feeding winter cabbage in the early part of 1931 to 17 rabbits for periods up to 114 days produced hyperplasia of the thyroid, but in only two instances were enlargements to more than twice the normal weight obtained. The microscopic changes were more conspicuous than the gross enlargement. The data obtained support the view of Webster, Marine and Cipra that there is an annual variation in the goiterogenic agent in cabbage, as well as seasonal differences and differences in the susceptibility of individual rabbits.

Cabbage and Goiter in Carpathian Ruthenia: A Contribution to Ethnic Pathology. By Prof. V. SUK, M.D., Ph.D. (Anthropologie, Prague, 1931, ix, 1-6.)

Goiter occurs endemically in many parts of the Carpathian Highlands; and the worst goiter centers are found in those poor villages where, during the unfavorable months of the year, more than two thirds of the population live to a great extent on cabbage, with the addition of potatoes, corn bread and oats. How great a part cabbage, which is utilized as boiled *sauerkraut*, plays in the dietary is indicated by the fact that a family of eight members may pickle as much as 1100 pounds for their own use. Examination of the children in this region showed a much higher incidence of goiter in the villages using excessive amounts of cabbage. This difference was especially evident among girls. Whereas 26.5 per cent of all the girls examined were without goiter, only 7.9 per cent of the girls in three villages using excessive amounts of cabbage were free from thyroid enlargement. Of all the girls, 9.4 per cent showed marked thyroid enlargement. For the three villages using much cabbage, the comparable figure was 15.8 per cent.

Torula Infection: A Review and Report of Two Cases. By JAMES W. WATTS, M.D. (Am. Jr. Path., 1932, viii, 167-192.)

Since Stoddard and Cutler pointed out the necessity of bearing torula infection in mind in patients with increased intracranial pressure without localizing signs, chronic meningitis, or other obscure cerebral conditions, the number of cases recognized has steadily increased. The first of the two here reported was in a woman, 32 years of age, in whom the infection was generalized although the symptoms were almost entirely cerebral. At autopsy a remarkable collection of pathological changes was found in the brain: diffuse meningitis, granulomas in the meninges, marked endarteritis and proliferation of adventitial elements of the meningeal vessels, an infarct in the pons, areas of softening in the cerebellum and various diffuse degenerative parenchymatous lesions. The second patient was a woman, 48 years of age, whose early complaints were headache, weakness and coldness of the extremities, inability to speak, and difficulty in swallowing. At autopsy numerous cystic cavities, from 1 to 8 mm. in diameter were found in the brain. This case therefore corresponds to the embolic order of lesions as classified by Freeman. The respiratory tract is probably the portal of entry in most cases.

Reviews

A Text-book of X-Ray Therapeutics. By ROBERT KNOX, completed and edited by WALTER M. LEVITT of the X-ray Department of St. Bartholomew's Hospital, London, England. 250 pages, 106 illustrations. The Macmillan Company, New York City, 1932. Price, $7.00.

At the time of his death Dr. Knox was engaged in the preparation of a comprehensive volume dealing with every branch of treatment by means of physical agents. However, only the sections concerning x-ray therapy were completed. These constitute an authoritative treatise on this subject as well as a memento of the work to which a great British radiologist devoted his energies for so many years. Dr. Levitt has very efficiently brought the text-book up to date, preserving the spirit of Dr. Knox's opinions on dosage and treatment, and keeping the balance between the claims of the more conservative therapists and the intensive methods of what might be called the newer school. Eight of the twenty chapters are entirely the work of Dr. Levitt. The subjects discussed are as follows: the effect of x-ray on tissues; the physics of x-ray therapy; x-ray measurements and dosage; the use of filters in x-ray therapy, with a description of the tubes and various types of high tension generators; the principles on which x-ray technique is based. About half of the text is devoted to these subjects, while the remainder is given over to a discussion of the various diseases in which the x-ray is of use as a therapeutic measure. Both the pathologist and the radiologist would be repaid by a careful study of the series of photomicrographs of pre- and post-radiation biopsies. The information on the physical and technical aspects has been presented in a simple, readable manner which meets the needs of the practical x-ray therapist and is more acceptable to the physician than if it were overloaded with scientific detail. The arrangement of the book is thoroughly logical, and the later chapters show a definite development from the physical and biological groundwork supplied in previous ones. The arrangement is excellent due to the careful outline and presentation of subject matter by organs and systems. A well chosen reference bibliography includes many classical articles which are of real value to the therapeutic radiologist. The book can be highly recommended as an excellent text for those who wish to learn some of the fundamental principles of x-ray therapy from a master. H.W.J.

Cytology and Cellular Pathology of the Nervous System. [By twenty-six contributors.] Edited by WILDER PENFIELD, Professor of Neurology and Neurosurgery, McGill University, Montreal. In three volumes. xiv + 1267 pages; 886 illustrations (15 in color). Paul B. Hoeber, Inc., New York City, 1932. Price, three volumes, $30.00

This beautifully printed work, in three volumes of convenient size, is uniform in style with Special Pathology, edited by E. V. Cowdry, and with McClung's Handbook of Microscopical Technique. It is, in fact, a group of monographs by 26 internationally-known specialists in the fields of neurocytology and neuropathology. The first two volumes deal with the more fundamental considerations of normal and pathological cytology of the nervous system, while the third volume considers neoplasms, malformations and hematogenous reactions. This work should be found in every medical reference library. In such, and in the hands of the specialist and advanced student it will find its greatest use. As is recognized in the preface it is not a complete treatise of the pathology of the nervous system. The pathology of the various disease entities is presented rather incidentally as part of the gen-

eral discussion and not under separate headings. Thus the reader may search the index in vain for the names of certain familiar diseases. Perhaps subsequent volumes may be added to the present series to fill in these gaps, which are in part due to the incomplete state of our knowledge.

An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum. By JOSEPH A. CAPPS, M.D., F.A.C.P., Professor of Clinical Medicine, University of Chicago; with the collaboration of GEORGE H. COLEMAN, M.D., F.A.C.P., Assistant Professor of Medicine, Rush Medical College. Foreword by ANTON J. CARLSON, M.D., Ph.D., Chairman of the Department of Physiology, University of Chicago. xiv + 99 pages, 33 illustrations. The Macmillan Company, New York City, 1932. Price, $3.00.

This book is the result of the wise application of the experimental method of scientific medicine to the daily practice of the art. When opportunity was offered by openings into the great body cavities, a silver wire passed through a hollow trochar was used to explore the pleural covering of lungs, chest wall and diaphragm, noting the presence or absence of pain and, when present, the exact location and character of the pain experienced. By a similar procedure the pericardial sac was explored when tapping for effusion, and likewise the peritoneum. The results of twenty years' application of this method are recorded in this small book. It thus becomes a unique contribution to the study of the significance of the localization of pain and of referred pain. It is compactly presented, simply written, and adequately illustrated. It should be read by all concerned with the diagnosis of disease of the chest and abdomen.

Clio Medica. VII. Medicine Among the American Indians. By ERIC STONE, M.D., xv + 139 pages, 17 illustrations. Paul B. Hoeber, Inc., New York City, 1932. Price, $1.00.

To American readers the seventh book in the Clio Medica series will prove of unusual interest. The convenient size of these low-priced medical historical monographs has already been commented upon in this section of the ANNALS. The present volume deals with the medical theories and practices of the American Indian. The material is presented in a highly interesting manner and the reading of this small volume will, for many, correct erroneous ideas about the intimate life of the Indian prior to the coming of the white man. Moreover, Indian Medicine had its own important effect upon the medicine of the pioneer whites. Much of our medical folklore has an Indian background; and the Indian is said to have added 59 drugs to our modern pharmacopeia. This book is a good coat-pocket companion for a short railway journey.

College News Notes

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J.—1 reprint;

Dr. I. D. Bronfin (Fellow), Denver, Colo.—1 reprint;

Dr. John E. Greiwe (Fellow), Cincinnati, Ohio—1 reprint;

Dr. Philip B. Matz (Fellow), Washington, D.C.—1 reprint;

Dr. Leon L. Solomon (Associate), Louisville, Ky.—5 reprints;

Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind.—1 reprint;

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa.—1 reprint;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints;

Dr. Norman Strauss (Associate), New York, N.Y.—1 reprint.

Dr. John Hyren Peck (Fellow), Des Moines, Iowa, was recently elected President of the National Tuberculosis Association.

At the recent annual meeting of the Medical Society of the State of North Carolina, at Winston-Salem, the following Fellows of the American College of Physicians gave papers as indicated:

Dr. Paul H. Ringer, Asheville—"Modern Trends in the Management of Tuberculosis";

Dr. S. M. Bittinger, Sanatorium—"A Brief Discussion, with Presentation of Several Types of Disease of the Lymphatic Glands Observed at the State Sanatorium";

Dr. S. D. Craig, Winston-Salem—"Iodized Salt, its Common Usage and and Results";

Dr. I. H. Manning, Chapel Hill—"The Contributions of Biological Chemistry to Clinical Medicine";

Dr. W. T. Rainey, Fayetteville—"Hypothyroidism";

Dr. L. B. McBrayer, Southern Pines—"Tuberculosis in Early Adult Life and its Prevention";

Dr. David T. Smith, Durham—"The Relation of Diet to Disease".

Dr. O. H. Perry Pepper (Fellow), Philadelphia, Pa., was a guest speaker at this meeting.

Dr. M. L. Stevens (Fellow), Asheville, completed his term as President of the Medical Society of the State of North Carolina at its recent meeting.

Dr. Isaac H. Manning (Fellow), Dean of the Medical Department of the University of North Carolina, Chapel Hill, was elected President-Elect, and will assume the office of President at the next annual meeting.

Dr. James B. Bullitt (Fellow), Professor of Pathology at the University of North Carolina, was elected President of the North Carolina Academy of Medicine at its thirty-first session at Wake Forest College.

Dr. William deB. MacNider (Fellow), Professor of Pharmacology, University of North Carolina, has recently been elected President of the American Society for Pharmacology and Experimental Therapeutics.

Dr. Joseph F. Paulonis (Fellow), Brooklyn, was recently appointed Pediatrician to the Mary Immaculate Hospital, Jamaica, New York.

Dr. E. Henry Jones (Fellow), Youngstown, Ohio, after pursuing postgraduate study in Dermatology and Syphilology, has abandoned his work in Internal Medicine and become Attending Dermatologist and Syphilologist to the Youngstown Hospital.

Dr. S. Calvin Smith (Fellow), Philadelphia, Pa., spoke on "The Clinical Significance of the Irregular Pulse" at a joint meeting of the Columbia, Lycoming and Montour Counties Medical Societies held at Bloomsburg (Pa.) Hospital, June 3.

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill., addressed the Carroll County Medical Society at Savanna, Ill., June 17, on "Respiratory Allergy".

Dr. Curran Pope (Associate), Louisville, Ky., delivered an address before the Louisville Society of Medicine on June 2; his topic being "Personal Observation and Studies of Pyretotherapy".

Dr. Louis F. Bishop (Fellow) and Dr. Louis F. Bishop, Jr. (Fellow), both of New York City, addressed the American Therapeutic Society at its Baltimore meeting in May on "A Study of Vertigo or Syncope in Association with Cardiovascular Disease", with lantern slide demonstration of cases.

Dr. A. W. F. Westhoff (Fellow), Richmond Hill, N.Y., was recently appointed Consultant to the Staff of the St. Cecilia Women's Hospital, Brooklyn.

Dr. W. McKim Marriott (Fellow), Dean and Professor of Pediatrics, Washington University School of Medicine, St. Louis, has accepted the visiting lectureship at the University of California Medical School for 1932-33.

Dr. Sidney J. Shipman (Fellow), San Francisco, Calif., has been made Associate Clinical Professor of Medicine at the University of California Medical School.

Dr. Oval N. Bryan (Fellow), Nashville, Tenn., was elected President of the Middle Tennessee Medical Association at its meeting in May.

Dr. Lewellys F. Barker (Fellow), Baltimore, Md., delivered the Commencement Address, May 31, at the University of Texas School of Medicine. Commencement Day marked the dedication at the University of Texas School of Medicine of its three new buildings, including a medical laboratory, the John Sealy Hospital Outpatient Building and the Rebecca Sealy Residence for Nurses.

The total cost of the three buildings was approximately $2,500,000. The laboratory building contains laboratories for histology, embryology, pathology, anatomy and experimental surgery, in addition to a musum of surgical pathology, a museum of general pathology, a library and two large lecture halls. The John Sealy Hospital Outpatient Building contains the administrative offices, x-ray department, surgical department, laboratories for basal metabolism and electrocardiography and clinics for ophthalmology, otolaryngology, obstetrics and gynecology; also laboratories, amphitheaters, nortuary room, animal houses, etc.

Dr. William A. White (Fellow), Washington, D.C., has been elected President of the International Congress on Mental Hygiene.

Dr. Charles F. Martin (Master), Montreal, has been elected a Vice President.

The second International Congress on Mental Hygiene will be held in Paris, France, during 1935.

Dr. Konrad E. Birkhaug (Fellow), Associate Professor of Bacteriology, University of Rochester School of Medicine, Rochester, N.Y., is in Paris studying at the Pasteur Institute. He will also spend some time in the study of art. A collection of water colors, bas-reliefs, masks and modeled figures by Dr. Birkhaug were recently exhibited at the Art Center in Rochester.

Dr. Edward B. Krumbhaar (Fellow), Philadelphia, Pa., and Dr. Ward J. MacNeal (Fellow), New York, N.Y., were elected President and Vice President, respectively, of the American Society for Cancer Research at the recent meeting of that organization.

Dr. Joseph M. King (Fellow), Los Angeles, was installed as President of the California Medical Association at its recent meeting in Pasadena.

Dr. Andrew C. Gillis (Fellow), Professor of Neurology, University of Maryland School of Medicine, Dr. Maurice C. Pincoffs (Fellow), Professor of Medicine, University of Maryland, and Dr. Robert H. Riley (Fellow), Director of the Maryland State Department of Health, all of Baltimore, have been appointed Consultants to the Baltimore Health Department.

Dr. Marcus W. Newcomb (Fellow), Browns Mills, N. J., was elected a Vice President of the Medical Society of New Jersey at its annual session in Atlantic City, June 17.

Dr. Howard T. Phillips (Fellow) Wheeling, W. Va., read a paper on "Diagnosis and Treatment of Prevalent Skin Diseases" at Logan, W. Va., before the Logan County Medical Society on August 19.

At the annual meeting of the 6th District Medical Society held at Baton Rouge, La., on July 14, Dr. Lester J. Williams (Fellow), of Baton Rouge was elected President and Dr. Cecil O. Lorio (Fellow) of Baton Rouge was elected Secretary-Treasurer.

On the scientific program were Dr. Philip H. Jones (Fellow) of New Orleans whose subject was "Some Consideration in Regard to Serums Proteins and Edema", and Dr. Cecil Lorio (Fellow) of Baton Rouge who presented a paper on "The Nervous Child and His Difficulties".

"The Newer Synthetic Drugs in the Treatment of Biliary Diseases", will be the title of a paper by Dr. Samuel Weiss (Fellow), New York City, which he will read at the International Congress on Biliary Lithiasis, at Vichy, France, Sept. 19-22, 1932.

Dr. Sidney A. Slater (Fellow), Worthington, Minn., has been re-elected to the Directorate of the National Tuberculosis Association for a two year term.

Dr. William Egbert Robertson (Fellow), who has held the Chair of Medicine for many years at Temple University School of Medicine, has been appointed Emeritus Professor of Medicine, and will devote much of his time to medical research. Dr. John A. Kolmer will succeed Dr. Robertson as Professor of Medicine, beginning with the autumn semester. Dr. Kolmer has resigned as Professor of Pathology and Bacteriology at the Graduate School of Medicine of the University of Pennsylvania.

At the regular meeting of the Western Oklahoma Medical Society, at Clinton, Okla., July 19, Dr. Lea A. Riely (Fellow), Oklahoma City, and Dr. Carroll M. Pounders (Fellow), Oklahoma City, delivered addresses on "Some of the Complications of Diabetes" and "Diarrheas of Infants and Children", respectively.

The University of Oklahoma conducted a postgraduate medical course in Degenerative Diseases for a period of four weeks during the summer. Dr. Wann Langston (Fellow), Oklahoma City, offered the course in Generalized Arterial Disease, Hypertension and Myocardial Disease; Dr. P. T. Bohan (Fellow), Kansas City, offered the course in Coronary Disaese and Angina Pectoris; Dr. C. J. Fishman (Fellow), Oklahoma City, offered the course in Vascular Disease of the Brain; Dr. Lea A. Riely (Fellow), Oklahoma City, offered the course in Peripheral Vascular Disease and Chronic Rheumatic Disease; Dr. A. W. White (Fellow) and Dr. J. T. Martin (Fellow), both of Oklahoma City, offered the course in Degenerative Disease on Basis of Food Deficiencies, Pellegra, Pernicious Anemia, etc.

Dr. John H. Peck (Fellow), Des Moines, Ia., headed a delegation of sixty American physicians to attend the Eighth Session of the International Union against Tuberculosis at the Hague and Amsterdam, September 6-9, 1932.

Dr. R. H. Kampmeier (Fellow), formerly Instructor in Internal Medicine at the University of Michigan Medical School, and more recently Internist at the Pueblo Clinic, Pueblo, Colo., has accepted an appointment as Assistant Professor of Medicine at the Louisiana State University Medical Center, New Orleans.

Dr. Frederick K. Herpel (Fellow), West Palm Beach, Fla., was recently elected Vice President of the Florida Radiological Society.

Dr. Cecil O. Lorio (Fellow), Baton Rouge, La., and Dr. Maud Loeber (Fellow), New Orleans, La., were elected President and Secretary-Treasurer, respectively, of the Louisiana State Pediatric Society at its last meeting.

Dr. John A. McIntosh (Fellow), San Antonio, Texas, was recently elected President of the Texas Neurological Society.

Dr. Charles G. Jennings (Master), Detroit, Mich., in June was the recipient of the degree of Doctor of Science from the College of the City of Detroit.

Dr. Delivan MacGregor (Fellow), Wheeling, W. Va., was elected President of the West Virginia Medical Association at its annual meeting in June.

Artificial Fever Produced by the Short Wave Radio and Its Therapeutic Application

By C. F. Tenney, M.D., F.A.C.P., *New York, N. Y.*

FOR the past fifteen years we have been interested in producing artificial fever as a therapeutic agent in the treatment of diseases of the peripheral circulation and arthritis by injecting a foreign protein intravenously, following the work of Petersen, Miller, and Lusk. This injection produces a chill within thirty minutes to an hour, followed by a rise in temperature of from two to five degrees; this in turn is followed by a sweat. The blood changes are an increase in the number of white blood corpuscles, as well as in the polymorphonuclears, and a slight variation in the chemical constitution of the blood and in blood pressures. In the treatment with the foreign protein the majority of cases complain that the chill is the most uncomfortable part of the reaction. It is also with some anxiety that a foreign protein is injected into the circulation.

In former times fever was induced by the application of external heat to the body, such as the tub-bath, hot packs, the electric cabinet, thermal baths in so called healing waters, and mud packs taken from mineral springs. It is common practice in England today to wrap the patient in hot, moist, blankets, putting on more blankets to lessen heat radiation and thus produce an increase in body temperature.

Doctors have observed that patients suffering from a chronic ailment are sometimes benefited by an intercurrent infection associated with a chill, fever, and sweat.

A new adjunct in the treatment of paresis in the past ten years, has been introduced by inoculating the patient with malarial parasites, which in turn produces chill, fever, and sweat, but with the detrimental effect of destruction of the red blood corpuscles, the subsequent weakening of the patient, and later having to cure the malaria. This treatment has, however, been most beneficial to these cases.

A newer form of producing hyperpyrexia is with the application of large diathermy plates to the trunk of the body, thus producing artificial fever. However, it is not a very comfortable jacket to wear.

Dr. W. R. Whitney, Director of the Research Laboratory of the General Electric Company, had noticed that the men working in the field with a short wave transmitter had a rise in temperature. He was interested in the work on paresis by Wagner-Jauregg and

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Presented at the San Francisco meeting of the American College of Physicians, April 6, 1932.

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